BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022

Writing group members

Laura Waters	Central and North West London NHS Foundation Trust
Alan Winston (Vice-chair)	Imperial College London and Imperial College Healthcare NHS Trust, London
Iain Reeves	Homerton Hospital NHS Trust, London
Marta Boffito	Chelsea and Westminster Hospital NHS Foundation Trust, London
Duncan Churchill	University Hospitals Sussex NHS Foundation Trust
Ben Cromarty	UK-CAB and Yorkshire Mesmac
David Dunn	University College London
Douglas Fink	London School of Hygiene and Tropical Medicine
Sarah Fidler	Imperial College London and Imperial College Healthcare NHS Trust, London
Caroline Foster	Imperial College Healthcare NHS Trust, London
Julie Fox	Guys and St Thomas' NHS Foundation Trust and Kings College London
Ravi Gupta	University of Cambridge
Andy Hilton	HiVitality and Positive Steps NW
Saye Khoo	University of Liverpool
Clifford Leen	NHS Lothian
Nicola Mackie	Imperial College Healthcare NHS Trust, London
Nadia Naous	Chelsea and Westminster Hospital NHS Foundation Trust, London
Mark Nelson	Chelsea and Westminster NHS Trust and Imperial College, London
Daisy Ogbonmwan	New Croft Centre, Newcastle upon Tyne
Chloe Orkin	Queen Mary University of London
Linda Panton	Western General Hospital, Edinburgh
Frank Post	King's College Hospital NHS Foundation Trust, London
Anton Pozniak	Chelsea and Westminster Hospital NHS Foundation Trust, London
Caroline Sabin	University College London
John Walsh (Chair)	Imperial College Healthcare NHS Trust, London

Contents

1 Introduction

1.1 Scope and purpose

The overall purpose of these guidelines is to provide guidance on best clinical practice for antiretroviral therapy (ART) and management of adults living with human immunodeficiency virus (HIV). The scope includes: (i) guidance on the initiation of ART in those previously naïve to therapy; (ii) support of people living with HIV on treatment; (iii) management of individuals experiencing virological failure; and (iv) recommendations for specific populations where other factors need to be taken into consideration. The guidelines are written for clinical professionals directly involved with and responsible for the care of adults living with HIV, and community advocates responsible for promoting the best interests and care of adults living with HIV. They should be read in conjunction with other published British HIV Association (BHIVA) guidelines. Of note, the term 'HIV' refers to HIV-1 throughout these guidelines.

1.2 Methodology

1.2.1 Guideline development process

BHIVA fully revised and updated the Association's guideline development manual in 2021 [REF]. 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) [REFS].

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. Details of the search questions and strategy (including the definitions of populations, interventions, comparisons and outcomes) are outlined in Appendix 2. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy were last published in 2015 [REF] with a subsequent interim update in 2016 to include tenofovir-AF, and interim statements in 2019 and 2022, to cover two-drug regimens and long-acting cabotegravir/rilpivirine respectively. For the 2022 guidelines Medline, Embase and the Cochrane library were searched between January 2014 (August 2014 for Virological failure/Transmitted drug resistance) and February/March 2020 (August 2019 for What to start). Abstracts from selected conferences were searched between January 2017 and September 2019. For further details see Appendix 2.

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

Commented [LW1]: BHIVA. *BHIVA Guideline Development Manual*. https://www.bhiva.org/file/jgCacHqmuxZFL/GuidelineDevelopmentManual.pdf

Commented [LW2]: Guyatt GH, Oxman AD, Kunz R *et al.* Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–1051. CHECKED & STILL LATEST
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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 were made by the writing group.

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 external peer reviews were commissioned.

1.2.2 Involvement of people living with HIV

BHIVA views the involvement of people living with HIV and community representatives in the guideline development process as essential. The writing group included two representatives appointed through the UK 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 have reviewed and commented on the guidelines.

1.2.3 GRADE

The GRADE Working Group [REF] 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.

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The advantages of the modified GRADE system are (i) the grading system provides an informative, transparent summary for clinicians, people living with HIV 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 clinicians, people living with HIV 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 people living with HIV. Most clinicians and individuals living with HIV 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 people living with HIV would want to follow a weak or conditional recommendation but many would not. Alternative approaches or strategies may be reasonable depending on the individual circumstances, preferences and values of the person living with HIV. 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 by 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 is high-quality evidence from consistent results from well-performed randomised controlled trials, 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 is 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 is 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 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 (GPPs), which are recommendations based on the clinical judgement and experience of the writing group. GPPs emphasise an area of important clinical practice for which there is no significant research evidence, nor is there likely to be any. 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 is deemed unacceptable. It must be noted that GPPs are not an alternative to evidence-based recommendations.

1.2.5 Dissemination and implementation

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

- E-publication on the BHIVA website and in the journal *HIV Medicine*;
- Shortened version detailing concise summary of recommendations;
- Shortened version for BHIVA guidelines app;
- Non-technical summary;
- E-learning module for continuing professional development;
- 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 fully updated and revised in 2027. 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 HIV-associated mortality and morbidity with a low level of drug toxicity. Treatment should improve the physical and psychological well-being of people living with HIV. The effectiveness and tolerability of ART has improved significantly over time. The overwhelming majority of people attending HIV services in the UK and receiving ART experience long-term virological suppression and good treatment outcomes [REF], which compare very favourably with other high-income countries. Of note, in 2020 around 99% of those diagnosed with HIV in the UK had initiated ART, with 97% of those on ART having a suppressed viral load [REF].

A UK analysis of individuals commencing ART between 2000 and 2010 demonstrated that life expectancy in men and women with an undetectable viral load and CD4 count greater than 350 cells/mm^3 is the same as, or slightly better than, that of the general population [REF]. Decreasing late diagnosis (and consequently

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starting ART earlier), maintaining individuals in care, reducing long-term drug toxicity and optimal management of comorbidities are crucial to ensure optimal outcomes for all people living with HIV.

A further benefit of ART is the reduction in HIV transmission. There is no risk of sexual transmission in the context of suppressive ART [REF]. The use of ART to prevent vertical transmission is universally accepted and best practice is addressed in the BHIVA guidelines for the management of HIV in pregnancy and postpartum [REF].

1.4 Resource use

ART is extremely cost-effective and is one of the most cost-effective medical interventions for long-term conditions [REFS].

There has been a steady decline in annual diagnoses of HIV since 2005 and the number of people living with HIV in the UK by the end of 2020 was estimated to be 106,890 (95% credible interval 105,460–109,510), of whom 5% were undiagnosed [REF]. Data on total ART spend are scant. It was estimated that the annual population treatment and care costs rose from £104 million in 1997 to £483 million in 2006, with a projected annual cost of £721 million in 2013 [REF]. However, data for England showed an antiretroviral (ARV) spend of £413.7 million in 2016/2017, a more than 3.5% saving compared to the previous year, despite higher numbers on treatment [REF]. This was driven by routine switching of branded to generic drugs, targeted value schemes and a relative reduction in the price of some branded products following the availability of generic drugs. Since then, costs in England have continued to decline further, to a predicted £270 million for 2022/2023 [REF], and it is likely that relative cost reductions have been similar in other UK nations. Balancing cost efficiency against the preferences of people living with HIV will continue to be a challenge and a continued collaborative approach between commissioners, healthcare professionals and people living with HIV 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 [REFS]. In addition to earlier diagnosis and initiation of ART, reducing inpatient episodes, decreasing drug toxicity, preventing HIV-associated comorbidities, streamlined monitoring and innovations in models of care are likely to have a beneficial effect on costs. However, the cost of ARV drugs remains the major factor contributing to treatment and care costs [REF]. With the increasing availability of generic drugs, commissioners and the NHS must continuously review the value and relative benefit of different drugs.

The writing group recognises that cost of drugs is an important ethical consideration in ART choice within a resource-constrained health economy which is free at the point of access. In addition to drug acquisition

Commented [LW8]: Prevention Access Campaign. Undetectable = Untransmittable. Available at: https://www.preventionaccess.org/undetectable. Accessed 24 March 2022.

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Commented [LW10]: Sendi PP, Bucher HC, Harr T *et al.* Cost effectiveness of highly active antiretroviral therapy in HIV-infected patients. Swiss HIV Cohort Study. *AIDS* 1999; **13**: 1115–1122.
Miners AH, Sabin CA, Trueman P *et al.* Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Med* 2001; **2**: 52–58.
Freedberg KA, Losina E, Weinstein MC *et al.* The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med* 2001; **344**: 824–831.
Yazdanpanah Y. Costs associated with combination antiretroviral therapy in HIV-infected patients. *J Antimicrob Chemother* 2004; **53**: 558–561.

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Beck EJ, Mandalia S, Lo G *et al.* Cost-effectiveness of early treatment with first-line NNRTI-based HAART regimens in the UK, 1996–2006. *PLoS One* 2011; **6**: e20200.

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costs there are costs associated with, for example, multidisciplinary team meetings, switching ART, comorbidities and management of drug–drug interactions. There are limited cost-effectiveness data in the UK comparing different ART options, and each nation undertakes separate drug procurement processes (securing different prices); for this reason, we did not include cost-effectiveness as an outcome in ART comparisons. 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 both clinicians and people living with HIV.

In developing the recommendations in these guidelines, we have considered differences in critical treatment outcomes between different drug regimens in determining recommended treatment regimens. Regimens no longer recommended for first-line therapy still have a role in terms of switching in virologically suppressed people and/or maintenance treatment in people already established on ART. We recognise that commissioning arrangements and local drug costs will influence ART choice where outcomes, across a range of clinical measures, are similar between individual drugs in the treatment of defined populations. We support regional and national prescribing algorithms based on cost where preferred options are recommended by BHIVA. 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. BHIVA is highly committed to the development and provision of HIV clinical trials to further improve ART options, and access to and participation in a clinical trial should be offered to people living with HIV where appropriate, considering the need to offer trials to women and racial minority groups.

2 Summary of recommendations

To be completed after consultation.

3 Active involvement of people living with HIV in decision-making

Recommendations

- We recommend that people living with HIV are given the opportunity to contribute actively to decisions about their treatment (GPP).
- Provision of treatment-support resources should include in-house, independent and community information providers and peer-support resources (GPP).
- We recommend following the European AIDS Clinical Society (EACS) guidance on 'assessing readiness to start and maintain ART' [REF] (GPP).
- We recommend that HIV services have clear pathways for referral to peer support (GPP).
- We recommend that people living with HIV share their status with general practitioners (GPs) and other healthcare professionals; where an individual declines to do so the benefits and potential harm should be reviewed regularly (GPP).

Auditable outcomes

- Percentage of people living with HIV who confirm they have been given the opportunity to contribute to decisions about their treatment.
- Percentage of people living with HIV who have been offered signposting or referral to peer support or treatment advocacy services.
- Evidence of signposting and/or referral to HIV peer support or treatment advocacy services.

Rationale

People living with HIV should be given the opportunity to consider and contribute to decisions about their treatment and the Medicines and Healthcare products Regulatory Agency now asks applicants to include evidence for patient involvement activities when submitting applications for selected new medicines [REF]. Studies show that trust in providers improves linkage to and retention in care and ART adherence [REF], that patient–provider relationship quality is associated with HIV-related and psychosocial outcomes [REF] and that trust transfers from offline to online health services [REF]. Having a consistent healthcare provider has been associated with better rates of viral suppression [REF].

Commented [CNS17]: **EACS** Readiness to Start/Maintain ART **https://eacs.sanfordguide.com/art/readiness-to-start-maintain-art**

Commented [LW18]: MHRA. MHRA pilots patient involvement in new applications https://www.gov.uk/government/news/mhra-pilots-patient-involvement-in-new-applications accessed April 2022

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Mitchell BD, Utterback L, Hibbeler P, Logsdon AR, Smith PF, Harris LM, Castle B, Kerr J, Crawford TN. Patient-Identified Markers of Quality Care: Improving HIV Service Delivery for Older African Americans. J Racial Ethn Health Disparities. 2022 Jan 21:1–12..

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Careful review of factors that impact adherence (see Section 6.1 Adherence) should be undertaken prior to ART initiation or switch.

Clinicians should establish what level of involvement the individual living with HIV would like, tailor their consultation style appropriately and ensure the individual has access to relevant information in line with BHIVA standards [REF]. If there is a question about an individual's capacity to make an informed decision, this should be assessed in line with General Medical Council guidance [REF].

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 [REF]. The following should be discussed:

- Rationale for ART;
- Potential adverse effects;
- Importance of adherence and the implications of missed/stopped ART;
- Social circumstances, options to store ART and ability to follow any necessary food requirements;
- Drug–drug interactions and where to seek advice.

Good care requires good communication with the GP and any clinicians involved in management of comorbid conditions. People living with HIV should be offered copies of any correspondence about them. Disclosure of HIV status to the GP should be considered best practice and the benefits of sharing HIV status with GPs and the potential risks of not doing so (such as drug–drug interactions) should be explained. However an individual's decision not to share their status with their GP should be respected but revisited regularly.

A systematic review of 20 randomised controlled trials showed that peer-support with routine medical care was superior to routine clinic follow-up, yielding better retention in care, ART adherence and viral suppression [REF]. Benefits for other outcomes such as mental health and quality of life were 'promising' but too uncertain to draw firm conclusions.

We recommend following the EACS guidance on assessing the readiness of people living with HIV to start and maintain ART [REF].

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4 When to start

4.1 Established infection

Recommendations

- We recommend that all people living with HIV should be on ART (Grade 1A).
- We recommend that readiness to start is assessed and decisions about starting ART tailored accordingly (GPP).

Auditable outcomes

- Proportion of diagnosed people living with HIV on ART.
- Proportion of people living with HIV not on ART where the rationale for this, and a discussion of the benefits of ART, has been documented at each visit.

Rationale

All consensus HIV treatment guidelines recommend immediate ART initiation, regardless of CD4 count, for people living with HIV based on:

- Randomised controlled trial evidence of benefit in terms of both HIV-related and non-HIV-related morbidity and mortality [REFS];
- Zero risk of sexual transmission of HIV in the context of sustained viral suppression [REF].

It is important to recognise that despite the significant reduction in relative risk of disease progression associated with early ART, the absolute risk associated with deferring ART was low. In START, 4.1% of individuals in the deferred arm versus 1.5% in the immediate treatment arm experienced a serious illness over 3 years of follow-up [REF]. The absolute risk of deferring therapy should be considered when making individual decisions.

People living with HIV should be counselled about the risks of interrupting treatment, in terms of individual health [REF], emergent drug resistance and risk of onward transmission.

4.2 Same-day ART initiation

Recommendations

- We recommend that the advantages and disadvantages of starting ART the same day as diagnosis are discussed with each person, including the lack of proven benefit for same-day ART in a UK or similar setting (GPP).

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Commented [CNS32]: El-Sadr WM, Lundgren J, Neaton JD et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006; 355: 2283–2296.

- We recommend same-day ART in the following situations (GPP):
  - Symptomatic primary HIV;
  - Where an individual wishes to and is ready to start same-day ART and this is clinically appropriate.

Rationale

With consensus established that ART should be offered immediately, the debate has shifted to how rapidly immediate ART should be commenced. In recent years, there has been increasing interest in the policy of starting ART very soon after diagnosis [REF]. The definition of rapid ART varies between studies, from the day of diagnosis to up to 2 weeks after diagnosis; additionally, even 'same day' may differ between studies depending on whether testing takes place at the same facility as treatment initiation. An analysis of four randomised controlled trials in low- and middle-income country settings concluded that same-day ART was associated with higher rates of viral suppression and retention in care at 12 months with a trend to lower mortality [REF]. The authors concluded that 'Accelerated ART initiation can lead to improved clinical outcomes and is likely to be of particular benefit in those settings where extensive patient preparation prior to starting ART results in long delays'. It is important to note that many screened participants were excluded from the trials included in the Ford analysis: a study conducted in Haiti [REF] excluded about half of screened participants, mainly for having World Health Organization (WHO) stage 3 or 4 disease. The results of randomised controlled trials may not translate to real-world settings. A cohort study conducted in Eswatini showed a higher risk of unfavourable outcomes among people who started ART the same day compared to those who started within 1 to 14 days [REF] and cohorts from South Africa [REF] and Ethiopia [REF] showed worse retention in care among people who started ART on the same day compared to later; despite this, the South African cohort (REF) showed lower mortality in people who started same-day ART.

Other potential benefits of rapid ART initiation include:

- Earlier reduction in viral load (and thus reduction in the potential risk of transmission of HIV) [REF];
- The potential empowerment of individuals through supporting them to start ART immediately if they choose to do so;
- Reduced mortality in low- and middle-income countries at 12 months was demonstrated in a meta-analysis of four same-day ART trials [REF] but a Cochrane review of seven studies including more than 18,000 patients showed no clear reduction in mortality [REF].

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Kerschberger B, Aung A, Mpala Q, Ntshalintshali N, Mamba C, Schomaker M, Tombo ML, Maphalala G, Sibandze D, Dube L, Kashangura R, Mthethwa-Hleza S, Telnov A, Tour R, Gonzalez A, Calmy A, Ciglenecki I.J Acquir Immune Defic Syndr. 2021 Dec 15;88(5):506-517.

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Commented [WLJ(ANWLN42]: Mateo-Urdiales A, Johnson S, Smith R, Nachega JB and Eshun-Wilson I. Rapid initiation of antiretroviral therapy for people living with HIV. The Cochrane database of systematic reviews. 2019; 6:CD012962.

However, some studies have shown no clear benefit of immediate ART initiation, and the applicability of results of studies conducted in very different settings to the UK, where engagement and retention in care is generally very high, is unclear. Data for same-day ART in the UK are lacking and a cohort study from London, often quoted as supporting this approach, which showed that rapid ART initiation was popular and feasible, did not examine same-day ART but rapid (within 8 days) versus less rapid (within 21 days) ART initiation [REF]. Of note, a French cohort study demonstrated worse retention in care at 1 year among people who started treatment earlier [REF]. Although this study did not specifically address same-day ART, and the results could be impacted by confounders, more studies are warranted.

Some individuals may be overwhelmed by an HIV diagnosis and while they process this information are unable to contemplate starting therapy immediately; it is important that they do not feel under pressure to start treatment if they are unprepared. A qualitative study among newly diagnosed people in Rwanda revealed that while participants supported a same-day approach, they described logistical and emotional challenges despite the perceived benefits [REF]. These challenges included trauma related to, and difficulty accepting, HIV diagnosis and feeling intimidated at the prospect of lifelong ART. Many reported significant side effects in the first days and weeks after initiating ART, 'likely reflecting either physiologic or psychosomatic adjustment to their medications' the authors concluded.

Rapid ART initiation is not recommended in the context of some opportunistic illnesses including cryptococcal meningitis [REF] and central nervous system (CNS) TB [REF]. There is insufficient evidence to establish whether same-day ART is appropriate in the context of TB symptoms [REF].

There are also potential benefits to deferring starting therapy until the results of baseline tests (including resistance test, baseline biochemistry, CD4 count and hepatitis B serology) are available; this can allow for a more tailored choice of ART regimen. A delay may also offer newly diagnosed individuals the opportunity to explore treatment options, access peer support, and prepare for starting a treatment where adherence is of paramount importance. Finally, the ability to offer same-day ART will depend on clinic facilities, staffing and capacity to offer the recommended support and assessments at the first visit.

4.3 Individuals presenting with AIDS or a major infection

Recommendation

Commented [WLJ(ANWLN43]: Whitlock G, Carbonell M, Blackwell S, Nwokolo N; Dean Street Collaborative Group. Rapid initiation of antiretroviral therapy in those with newly diagnosed HIV infection in London, UK. HIV Med. 2019 Nov;20(10):699-703.

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Commented [CNS47]: Bracchi M, van Halsema C, Post F *et al*. British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2019. *HIV Med* 2019; **20 Suppl 6**: s2-s83.

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- We recommend that most individuals presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 count <200 cells/mm^3, start ART within 2 weeks of initiation of specific antimicrobial chemotherapy (Grade 1B).

Auditable outcome

- Proportion of individuals living with HIV presenting with an AIDS-defining infection or with a serious bacterial infection and a CD4 count <200 cells/mm^3 who are started on ART within 2–4 weeks of initiation of specific antimicrobial chemotherapy.

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, interquartile range [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 TB as the primary infection were excluded from this study, and the majority of individuals enrolled had Pneumocystis pneumonia. All 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 patients with HIV who are started on ART while in the intensive care unit [3,4], but the data are insufficient to make a recommendation for 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 is warranted 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 cerebrospinal fluid (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.

While most studies in all settings favour deferred (after 2 weeks) intitiation of ART during treatment of cryptococcal meningitis, timing of ART initiation after 2 weeks should be tailored to individual cases supported by careful clinical and CSF assesments.

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4.4 Treatment of primary HIV infection

Recommendation

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

Auditable outcomes

- Proportion of individuals with PHI assessed by an HIV specialist within 2 weeks.
- Proportion of individuals with PHI offered ART as soon as possible after confirmed HIV status.

Rationale

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 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]. However these studies were not powered to determine specifically the outcome of those starting ART at the time of PHI diagnosis versus deferral.

In the context of PHI there are additional issues to take into account when considering best management. PHI is a distinct situation in which 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 cell counts [6,7], high plasma viral loads (>100,000 copies/mL) [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 diagnosis of PHI, and hence early ART initiation should be prioritised [REF]. A recent Italian study identified enhanced clinical outcome among a cohort of participants recently diagnosed with HIV [REF]. Early ART emerged as an independent predictor of optimal immunological recovery after adjustment for baseline CD4 (absolute and percentage count) and CD4/CD8 ratio.

ART should be started only when the individual feels ready. Certain ART combinations may be better tolerated in association with symptoms of PHI. The only independent predictor of first-line ART discontinuation was an initial ART regimen including more than three drugs [REF], and complex ART regimens were associated with worse virological responses [REF]. 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 (Grade 1D);
- Any AIDS-defining illness (Grade 1A);
- CD4 count <350 cells/mm^3 (Grade 1C);
- PHI diagnosed within 12 weeks of a previous negative test (Grade 1C).

The advantages and disadvantages of early ART initiation with a view to long-term therapy should be clearly and sensitively presented to any individual diagnosed with PHI (see Table 4.1). Once started, ART 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. The recent global use of INSTI-containing ART regimens has limited the prevalence of transmitted drug-resistant HIV variants among individuals with PHI, however baseline viral sequencing is recommended at the time of diagnosis [REF].

Table 4.1 Advantages and disadvantages of starting ART in PHI

Advantages of starting ART in PHI	Disadvantages 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

Commented [FSJ49]: https://pubmed.ncbi.nlm.nih.gov/32258852/
Muscatello A, Nozza S, Fabbiani Met al; Inaction Study Group.. Enhanced Immunological Recovery With Early Start of Antiretroviral Therapy During Acute or Early HIV Infection-Results of Italian Network of ACuTe HIV InfectiON (INACTION) Retrospective Study. Pathog Immun. 2020 Feb 24;5(1):8-33.

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Guo C, Wu Y, Zhang Y, Liu X, Li A, Gao M, Zhang T, Wu H, Chen G, Huang X.
Front Pharmacol. 2021 Nov 24;12:718763.

Reduced risk of onward viral transmission at a time of very high viral load and consequent high risk of transmission [19-24]	Consider choice of ART regimen in the context of symptoms of PHI, in particular widespread skin rash, fevers or lymphadenopathy gastrointestinal symptoms
Reduction in morbidity and more rapid disease progression associated with high viraemia [8]	
Data from the START, TEMPRANO and HPTN052 trials showed 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 is deferred [REF]	

Commented [FSJ54]: Benefits of antiretroviral therapy initiation during acute HIV infection.
De Clercq J, Rutsaert S, De Scheerder MA, Verhofstede C, Callens S, Vandekerckhove L.
Acta Clin Belg. 2022 Feb;77(1):168-176

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

- Preservation of immune function, in terms of both total CD4 counts and the ratio of CD4:CD8 T cells (which reflects immune activation and is associated with increased all-cause mortality), is 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 the high viral load of PHI [REF].

Commented [FSJ55]: Clinical and public health implications of acute and early HIV detection and treatment: a scoping review.
Rutstein SE, Ananworanich J, Fidler S, Johnson C, Sanders EJ, Sued O, Saez-Cirion A, Pilcher CD, Fraser C, Cohen MS, Vitoria M, Doherty M, Tucker JD.
J Int AIDS Soc. 2017 Jun 28;20(1):21579

There is never likely to be a randomised controlled trial in PHI comparing immediate versus deferred ART that is powered to a survival outcome, as such a study would require decades to accrue endpoints and given the level of evidence supporting ART initiation would not be ethical. 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 the immune system [REF] 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 diagnosis of PHI; therefore, even outside the circumstances where prompt ART is advised, starting within 1 year of PHI diagnosis is advisable [18].

Commented [FSJ56]: Evolution and Diversity of Immune Responses during Acute HIV Infection.
Kazer SW, Walker BD, Shalek AK.
Immunity. 2020 Nov 17;53(5):908-924.

Immediate or expedited ART initiation for symptomatic seroconversion and for 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 that a clear and informed discussion of the advantages and disadvantages of immediate ART is provided to all individuals to support them making the optimal treatment decision. An individual's readiness to start ART should be explored prior to commencing treatment (see Section 3 Active involvement of people living with HIV in decision-making).

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4.5 Impact of treatment on prevention of onward transmission

Recommendations

- An assessment of the risk of transmission to others should be made at diagnosis and subsequent visits with signposting to relevant interventions (GPP).
- We recommend that the evidence that treatment with suppressive ART reduces the risk of sexual transmission to zero is discussed with all people living with HIV (GPP).
- We recommend that the major impact of suppressive ART on the risk of vertical transmission and transmission through breastfeeding is discussed with all people living with HIV (GPP).
- We recommend condoms, both male and female, to reduce the risk of other sexually transmitted infections and unplanned pregnancy, where appropriate (GPP).

Auditable outcomes

- Proportion of people for whom the risk of transmission has been assessed at diagnosis and regularly thereafter.
- Proportion of people who have a discussion that suppressive ART means a zero risk of onward sexual transmission (undetectable=untransmittable) and a very low risk of vertical transmission or transmission through breast milk is documented in the medical notes.

- Proportion of people for whom a discussion about the benefits of condoms and other modalities to prevent sexually transmitted infections and unintended pregnancy has been documented.
- Proportion of people for whom advice that viral suppression should be confirmed after initiation and that high and consistent adherence to ART is required to maintain viral suppression has been documented.

Rationale

The potential effect of HIV treatment to reduce the risk of onward sexual transmission should be discussed with all people living with HIV as a part of combination prevention.

Cohort studies provided the initial evidence base for treatment to reduce transmission with no, or very rare, transmission events within heterosexual, serodifferent couples where the HIV-positive partner had an undetectable viral load on treatment [REFS].

This was followed by good evidence from one randomised controlled trial (HPTN 052) [REF] which showed that ART yielded a 96% reduction in transmission to HIV-negative partners and zero transmissions when the HIV-positive partner had an undetectable viral load. Secondary outcomes of the Partners in Prevention trial [REF] demonstrated similar findings. Of note, 97% of couples participating in HPTN 052 and all couples participating in Partner in Prevention were heterosexual.

Three large prospective cohort studies have also investigated the risk of sexual HIV transmission in the context of suppressive ART: PARTNER (heterosexual people and men who have sex with men [MSM]), PARTNER2 (MSM) and Opposites Attract (MSM) [REFS]. These three studies demonstrated no sexual transmission to HIV-negative partners when the HIV-positive person was on suppressive ART. These studies provide sufficient evidence, after tens of thousands of condomless sex acts among MSM, to conclude that there is zero risk of onward sexual transmission of HIV in the context of viral suppression [REF].

Condoms should still be recommended to reduce the risk of other sexually transmitted infections and unwanted pregnancy.

People living with HIV 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 (INSTIs) are characterised by more rapid viral suppression with most individuals achieving an undetectable viral load by 1–3 months [REFS]. People living with HIV 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.

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OPPOSITES ATTRACT: Bavinton BR, Pinto AN, Phanuphak N et al; Opposites Attract Study Group. Viral suppression and HIV transmission in serodiscordant male couples: an ...

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People wishing to conceive can be reassured that there is zero risk of transmission if the HIV-positive person has a durably suppressed viral load. Sperm washing is not recommended in the context of viral suppression [REF].

Pre-exposure prophylaxis (PrEP) is not recommended for HIV-negative people with an HIV-positive sexual partner on suppressive ART unless they have other sexual partners who may have HIV with a detectable viral load [REF]. The use of ART to prevent vertical transmission is discussed in the BHIVA guidelines for the management of HIV in pregnancy and postpartum [REF].

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Commented [LW65]: BHIVA guidelines for the management of HIV in pregnancy and postpartum 2018 (2020 third interim update)

4.6 Persons choosing not to commence ART

Recommendations

- We recommend that all people living with HIV choosing not to commence ART should be counselled about the risk to their own health and the risk of onward sexual transmission of HIV (Grade 1A).
- We recommend that in all people living with HIV choosing not to commence ART, capacity to make this decision is assessed and psychological support offered (GPP).
- We recommend that where people with HIV have chosen to not commence ART, their sexual partners are signposted to prevention interventions including PrEP (GPP).

Rationale

The advantages of commencing ART in all people living with HIV are outlined above. In people living with HIV who choose not to commence ART, healthcare providers should assess the rationale for this choice. Such assessments should include exploring the underlying reasons and ensuring the individual is aware of the risks of this choice to their own health, and to the health of others with regard to onward sexual transmission of HIV in those who are sexually active.

Assessment of capacity should be undertaken to ensure that the individual understands the risks of not commencing ART and psychological support offered if deemed required. Further management may be based on recommendations from psychological assessment; for instance, the potential to offer behavioural interventions.

The START study results can be used to counsel people choosing not to take ART [REF]. For people with a CD4 count greater than 500 cells/mm^3, early ART was associated with significant reduction in relative risk of disease progression but the absolute risk of deferring ART was relatively small; 4.1% of individuals in the

Commented [LW66]: INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015; 373: 795–807.

deferred arm versus 1.5% in the immediate treatment arm experienced a serious illness over 3 years of follow-up. The absolute risk of deferring therapy can help guide individual decisions.

It is important that all people living with HIV who choose not to commence ART should be offered regular follow-up appointments at approximately 3-monthly intervals, or at shorter intervals if deemed clinically appropriate. This is to ensure that discussions about commencing ART are ongoing, and also to monitor for HIV-disease progression.

4.7 Considerations when managing people with spontaneous HIV viral control

4.7.1 Definition of viral controllers (also known as elite controllers)

Viral controllers are defined as:

- Individuals with confirmed HIV infection by positive HIV antibody test (western blot), or HIV RNA or DNA detected through routine NHS or referral centre testing *and*
- Individuals with confirmed HIV-1 infection not taking ART with HIV viral load <50 copies/mL on more than one occasion *and*
- Individuals with confirmed HIV infection not on ART with CD4 count in the normal range and/or CD4:CD8 ratio >1.0.

Starting ART should be discussed with all people living with HIV and should be commenced for anyone wishing to start treatment irrespective of their HIV viral load and CD4 count. This section refers only to those rare individuals who spontaneously control HIV viral load to undetectable levels (<50 copies/mL) without ART, and have repeated CD4 counts in the normal range where the benefits of ART remain uncertain. Specialist consultation through referral to a national NHS clinical service (IDRIS; clinic run at Imperial College NHS Trust, London) via PHE is recommended (csuqueries@phe.gov.uk).

Recommendations

- Given that there is evidence of ongoing HIV replication even at a low level in some viral controllers, ART is strongly recommended for viral controllers with evidence of HIV disease progression, defined by declining CD4 counts, inverted CD4:CD8 ratio (<1) or the development of HIV-related complications (Grade 2A).
- In specific situations there may be a case to continue regular HIV viral load and CD4 count monitoring while remaining off ART; we recommend this only where the following have been excluded (GPP):

- Chronic co-infection with hepatitis B or C, or human T-cell lymphotropic virus (HTLV);
- Significant past or present comorbidities such as cancer, autoimmune disease and cardiovascular disease (CVD; myocardial infarction and cerebrovascular accident);
- Indication for current or planned immune suppressive or chemotherapy treatment;
- Pregnancy or planned pregnancy and breastfeeding; this is due to the relative immune suppression of pregnancy plus uncertainty of viral rebound and potential risk of transmission. Stopping ART post-delivery must be discussed with a specialist team.

Recommendations for monitoring of viral controllers off ART (GPP):

- Measurement of HIV viral load 6- to 12-monthly;
- Measurement of CD4 count and CD4:CD8 ratio at least 6-monthly;
- Clinical assessment at least 6-monthly for CVD, malignancy, any comorbidity, pregnancy and hepatitis co-infection.

Rationale

In a rare group of people living with HIV, estimated to represent approximately 1–5% of all those with HIV depending on the definition [REFS], HIV viral control to undetectable levels can be achieved without ART. The START [REF] and TEMPRANO [REF] studies demonstrated that initiating ART confers survival benefit for all people living with HIV regardless of CD4 count; therefore, delaying ART to see if an individual becomes a viral controller is **strongly discouraged**. The START study did include several participants with viral loads less than 3000 copies/mL, including 93 with undetectable viraemia. A separate analysis of this population demonstrated higher CD4 counts, greater proportion with suppressed viremia, and decreases in D-dimer levels on immediate ART but a lack of difference in serious clinical outcomes [REF]. These data support immediate ART in people with low-level viraemia, although equipoise remains for suppressors. There remains uncertainty as to the best management of long-term viral controllers.

4.7.2 Risks versus benefits of ART in viral controllers

The risk of HIV clinical progression among viral controllers has been estimated from observational studies. A French longitudinal study of 302 viral controllers over a median of 14.8 years demonstrated that 30% clinically progressed and started ART [REFS]. Whether viral controllers are still at risk of HIV-associated comorbidities and could potentially benefit from ART is still debated, although studies have demonstrated an increased risk of hospitalisation among viral controllers compared with matched uninfected individuals [REF].

Commented [LW67]: Grabar S, Selinger-Leneman H, Abgrall S. Prevalence and comparative characteristics of long-term nonprogressors and HIV controller patients in the French Hospital Database on HIV. *AIDS* 2009; **23**: 1163–1169. Sajadi MM, Constantine N, Abgrall S *et al*. Epidemiologic characteristics and natural history of HIV-1 natural viral suppressors. *J Acquir Immune Defic Syndr* 2009; **50**: 403–408.

Commented [LW68]: INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015; 373: 795–807.

Commented [LW69]: TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808-22.

Commented [LW70]: Sereti I, Gulick RM, Krishnan S, Migueles SA, Palfreeman A, Touzeau-Römer V, Belloso WH, Emery S, Law MG; INSIGHT START Study Group. ART in HIV-Positive Persons With Low Pretreatment Viremia: Results From the START Trial. J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):456-462.

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Okulicz JF, Marconi VC, Ladrum ML *et al*. Clinical outcomes of elite controllers, viremic controllers and long term non-progressors in the US Department of Defense natural history study. *J Infect Dis* 2009; **200**: 1714–1723.
Plaçais L, Boufassa F, Lécuroux C *et al*.; ANRS CO21 study group. Antiretroviral therapy for HIV controllers: Reasons for initiation and outcomes in the French ANRS-CO21 CODEX cohort. EClinicalMedicine 2021; **37**: 100963.

Commented [LW72]: Crowell TA, Gebo KA, Blankson JN *et al*.; HIV Research Network. Hospitalization rates among HIV elite controllers and persons with medically controlled HIV infection. *J Infect Dis* 2015; 211: 1692–1702

There is an established relationship between clinical outcomes and excessive immune activation, reversal of CD4:CD8 ratio and age, in particular in CVD and malignancy [REF]. Some viral controllers with normal CD4 counts show evidence of abnormally high immune activation and surrogate markers of atherosclerosis [REFS], which may contribute to an increased risk of non-AIDS-related diseases. In a study of 30 viral controllers and 187 ART-treated people living with HIV, all of whom had undetectable HIV viral load measurements, viral controllers had higher levels of CD4+ and CD8+ immune activation (P<0.001 for both) compared with ART-treated people living with HIV which could contribute to progressive CD4 cell loss and comorbidities despite undetectable plasma viral load [9]. Among viral controllers with elevated T cell activation, ART has been demonstrated to normalise these parameters [12]. Moreover, viral controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial [REFS], although all studies have been small and long-term outcomes are not yet known.

Whether a potential immunological benefit of ART in viral controllers outweighs the potential risks of ART toxicity and results in clinical benefit is unclear and the US Department of Health and Human Services (DHHS) guidelines state that there is insufficient evidence to adequately compare risks and benefits of ART in viral controllers [REF]. It is unlikely that randomised controlled trials will be conducted, given the very low prevalence of viral controllers. It is well established that there is no risk of sexual transmission from a person living with HIV receiving ART with an undetectable plasma HIV viral load for >6 months. Although the risk of transmission of HIV from a viral controller not receiving ART to a sexual partner is therefore likely to be very low or zero, there are no robust data in this setting. no transmission has ever been confirmed, with only one possible transmission reported in this context [REF].

Commented [LW73]: Serrano-Villar S, Pérez-Elías MJ, Dronda F *et al*. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. *PLoS One* 2014; **9**: e85798.

Commented [LW74]: Hunt PW, Benchley J, Sinclair E *et al*. Relationship between T cell activation and CD4$^+$ T cell count in HIV-seropositive individuals with undetectable HIV RNA levels in the absence of therapy. *J Infect Dis* 2008; **197**: 126–133.
Pereyra F, Lo J, Triant VA *et al*. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. *AIDS* 2012; **26**: 2409–2412.

Commented [LW75]: Sedaghat AR, Rastegar DA, O'Connell KA *et al*. T cell dynamics and the response to HAART in a cohort of HIV-1 infected elite suppressors. *Clin Infect Dis* 2009; **49**: 1763–1766.
Karris MY, Haubrich RH. Antiretroviral therapy in the elite controller: justified or premature? *J Infect Dis* 2015; **211**: 1689–1691.

Commented [LW76]: DHHS - https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines accessed 29 April 2022

Commented [FSJ77]: Killian et al.: Possible transmission of human immunodeficiency virus-1 infection from an elite controller to a patient who progressed to acquired immunodeficiency syndrome: a case report. Journal of Medical Case Reports 2012 6:291.

4.7.3 Summary

There is a clear rationale for offering ART even in the absence of detectable plasma HIV RNA levels. If ART is withheld, people with spontaneous viral control should be followed closely, as some may experience CD4 cell count decline, loss of viral control or complications related to HIV infection.

Overall the quality of evidence remains low and current recommendations are based on expert opinion. Enrolment in cohort studies or clinical trials for people with spontaneous viral control should be offered where available.

4.8 Stopping therapy

Recommendation

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

Auditable outcomes

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

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 trials, subjects were randomly allocated to either CD4 cell count-guided intermittent therapy (stopping ART once CD4 count >350 cells/mm^3, restarting when CD4 count falls to 250 cells/mm^3) or continuous ART [4]. The trial showed that intermittent therapy was associated with a significantly higher rate of opportunistic disease and all-cause mortality and a higher rate of major CVD or 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 comorbidities 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 person with HIV, it should be continued. Interruptions of ART should only be considered in exceptional circumstances. These may include:

- Severe drug toxicity (e.g. hepatotoxicity);
- Severe psychological distress;
- Severe intercurrent illness or major organ dysfunction.

For guidance on pharmacokinetic considerations when stopping ART (see Section 6.2.2 Stopping therapy: pharmacological considerations).

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. Cardiello 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.

5 What to start

5.1 Introduction

Following the GRADE process, as in the previous 2015 BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy [REF], clinical outcomes were discussed and ranked according to importance by the writing group (critical, important and not important). A list of 10 outcomes, broadly reflecting virological outcomes and adverse events, were considered for these guidelines. In the previous guidelines [REF], virological success outcomes were ranked the highest, but in developing the present guidelines, virological failure and resistance were considered to be more important, given the high rates of virological success of most of the recommended regimens, as well as the impact of these outcomes on subsequent treatment. Adverse event outcomes also moved higher up in the ranking, owing to the importance of tolerability for long-term treatment. The outcomes and ranking were as follows:

Commented [CNS78]: BHIVA 2015 Treatment guidelines

Commented [CNS79]: BHIVA 2015 Treatment guidelines

Critical outcomes:

1. Proportion with virological failure at week 48
2. Proportion developing resistance at virological failure
3. Proportion discontinuing treatment due to an adverse event
4. Proportion with virological success at week 48
5. Proportion with virological success at week 96

Important outcomes:

6. Proportion with a drug-related serious adverse event
7. Proportion with any serious adverse event
8. Proportion with drug-related grade 3/4 adverse events
9. Proportion with virological failure at week 96
10. Proportion with any grade 3/4 adverse event

Relevant randomised clinical trials identified from the literature search were evaluated according to these outcomes with a meta-analysis, forest plots and GRADE tables (see Appendix 3). This evaluation is referred to as the 'GRADE analysis' in the rationale for the treatment recommendations.

Of note, the recommendations in this section are for first-line therapy; there are several regimens not recommended first line but which are suitable for switch or to continue when clinically appropriate. For further details see Section 5.10 Suppressed switch or maintenance.

The BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals should be consulted for guidance on assessment of people living with HIV before initiation of ART and monitoring individuals on ART [REF]. The monitoring guidelines recommend that all newly diagnosed individuals should have a baseline genotypic resistance test. Implications on the selection of first-line ART if baseline viral resistance is detected are discussed in Section 6.2.4 TDM.

Commented [LW80]: BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals 2016 (2019 interim update)

Recommendations

Recommendations for choice of first-line ART are summarised in Table 5.1.

Table 5.1 Recommendations for choice of first-line ART

Recommended as initial treatment for most people living with HIV (Grade 1A)	
Tenofovir-DX/emtricitabine or tenofovir-AF/emtricitabine with dolutegravir	
Abacavir/lamivudine/dolutegravir	HLA B*5701 negative and estimated 10-year risk of CVD less than 10%
Tenofovir-AF/emtricitabine/bictegravir	
Dolutegravir/lamivudine	No baseline lamivudine resistance Baseline viral load less than 500,000 copies/mL Baseline CD4 count greater than 200 cells/mm^3 No active hepatitis B infection and if at risk of hepatitis B, hepatitis B virus immune
Recommended as initial treatment in certain clinical situations (Grade 2A)	
Tenofovir-DX/emtricitabine or tenofovir-AF/emtricitabine with raltegravir	Baseline viral load less than 100,000 copies/mL
Tenofovir-DX/emtricitabine or tenofovir-AF/emtricitabine with darunavir/ritonavir or darunavir/cobicistat	
Tenofovir-DF/lamivudine/doravirine or tenofovir-DX/emtricitabine or tenofovir-AF/emtricitabine with doravirine	
Tenofovir-DX/emtricitabine or tenofovir-AF/emtricitabine or abacavir/lamivudine with efavirenz	May be a first-line choice in pregnancy and for people on TB treatment but not recommended outside these scenarios

Where a woman living with HIV is pregnant, or planning to conceive, the BHIVA pregnancy guidelines should be followed [REF].

5.2 Regimens recommended for most people

The INSTI-based three-drug combinations recommended first line have been compared in large, high-quality randomised controlled trials with at least one other preferred regimen, or with efavirenz or boosted darunavir-based treatment.

- Dolutegravir with abacavir/lamivudine or tenofovir-DX/emtricitabine has compared favourably on a number of critical outcomes when compared with efavirenz- [REF] or boosted darunavir-based regimens [REF].
- Tenofovir-AF/emtricitabine/bictegravir has been compared with abacavir/lamivudine/dolutegravir [REF] and with tenofovir-AF/emtricitabine with dolutegravir [REF]. No significant differences for any critical outcome were demonstrated in either of these comparisons.
- Tenofovir-DF/emtricitabine with dolutegravir has been compared with the novel two-drug combination of dolutegravir/lamivudine, demonstrating comparable results for critical outcomes [REF].

5.2.1 Dolutegravir versus efavirenz

Dolutegravir with two nucleoside reverse transcriptase inhibitors (NRTIs) has been compared with efavirenz with two NRTIs for first-line treatment in the ADVANCE, NAMSAL and SINGLE studies [REFS]. In the meta-analysis conducted for these guidelines there were overall differences in favour of dolutegravir for virological success, adverse event-driven discontinuation, and both overall and drug-related Grade 3 and 4 adverse events. Virological failure was not significantly different, but there was a trend towards increased development of resistance at failure for the efavirenz-based combinations.

- The ADVANCE study was a large, open-label, randomised comparison of two dolutegravir-based regimens, with either tenofovir-DF/emtricitabine or tenofovir-AF/emtricitabine, and a third arm comprising tenofovir-DF/emtricitabine/efavirenz [REF]. At week 48, this trial demonstrated non-inferiority of each arm, according to a pre-specified significance level. However, 85% of those taking tenofovir-DF/emtricitabine/dolutegravir had a viral load <50 copies/mL, compared with 79% of those taking tenofovir-DF/emtricitabine/efavirenz, and adverse event-related discontinuation was an important factor accounting for this difference.
- The SINGLE study was a large, double-blind randomised comparison of abacavir/lamivudine/dolutegravir and tenofovir-DF/emtricitabine/efavirenz [REF]. In this study, at

Commented [CNS81]: BHIVA Pregnancy guidelines Gilleece Y, Tariq S, Bamford A *et al*. British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018. *HIV Med* 2019; **20 Suppl 3**: s2-s85.

Commented [LW82]: SINGLE: Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; 369:1807–1818. ADVANCE Venter WDF, Moorhouse M, Sokhela S et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019 Aug 29;381(9):803-815. NAMSAL: Calmy A, Tovar Sanchez T, Kouanfack C et al; New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 Study Group. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. Lancet HIV. 2020 Oct;7(10):e677-e687.

Commented [LW83]: FLAMINGO Clotet B, Feinberg J, van Lunzen J et al; ING114915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014 Jun 28;383(9936):2222-31.

Commented [LW84]: GS-1489: Gallant J, Lazzarin A, Mills A et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017 Nov 4;390(10107):2063-2072.

Commented [LW85]: GS-1490 - Sax PE, DeJesus E, Crofoot Get al. Coformulated bictegravir, emtricitabine, tenofovir alafenamide after initial treatment with bictegravir or dolutegravir and emtricitabine/tenofovir alafenamide. AIDS. 2018 Jul 31;32(12):1723-1725.

Commented [LW86]: GEMINI - Cahn P, Madero JS, Arribas JR et al. Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials. J Acquir Immune Defic Syndr. 2020 Mar 1;83(3):310-318. ...

Commented [LW87]: SINGLE: Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; 369:1807–1818. ...

Commented [LW88]: ADVANCE - Venter WDF, Moorhouse M, Sokhela S et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019 Aug 29;381(9):803-815.

Commented [LW89]: SINGLE - Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; 369:1807–1818. ...

week 48, there was clear superiority for viral load outcomes favouring dolutegravir and again there were significantly more adverse event-related discontinuations in those taking efavirenz.

- NAMSAL was an open-label randomised comparison of dolutegravir-based treatment with lower-dose efavirenz (400 mg) [REF]. Viral suppression at week 48 was non-inferior with a numerical advantage for dolutegravir (74.5% *vs* 69%).

The week 96 results of the above studies were in accord with the week 48 results. However, the ADVANCE study also reported more failure with resistance at week 96 in those taking efavirenz-based regimens (13 of 21 participants taking efavirenz with virological failure and resistance data, *vs* 2 of 28 taking dolutegravir).

5.2.2 Dolutegravir versus bictegravir

The fixed-dose combination tenofovir-AF/emtricitabine/bictegravir has been compared in large, high-quality, randomised controlled trials with tenofovir-AF/emtricitabine and dolutegravir (GS-US-380–1490), as well as with abacavir/lamivudine/dolutegravir (GS-US-380-1489) [REFS]. Both studies were double-blind. In addition,both studies established non-inferiority for virological success and there were no important differences in any of the critical outcomes considered by the writing group. Of those that experienced virological failure, no resistance was detected in any arm.

5.2.3 Dolutegravir/lamivudine

Once-daily dolutegravir in combination with lamivudine as first-line treatment has been compared with standard triple therapy in two Phase 3 randomised clinical trials (GEMINI 1 and 2) [REF]. Both studies compared dolutegravir/lamivudine with dolutegravir and tenofovir-DF/emtricitabine. Investigators and participants were blinded to study drug allocation as the lamivudine and tenofovir-DF/emtricitabine were over-encapsulated to be visually similar. Across the two studies, 1441 participants were randomly assigned to treatment. Non-inferiority of the two-drug regimen to the three-drug regimen was demonstrated in both studies at both week 48 and week 96 (viral load <50 copies/mL at week 48 by intention-to-treat analysis, for two-drug *vs* three-drug: GEMINI 1, 90% *vs* 93%; GEMINI 2, 93% *vs* 94%). People with a pre-treatment viral load >500,000 copies/mL were excluded, as were those with hepatitis B co-infection, pre-existing antiretroviral resistance to lamivudine and opportunistic disease (other than cutaneous Kaposi's sarcoma with a CD4 count >200 cells/mm^3) and pregnant women. Baseline INSTI resistance testing was not undertaken. The viral load exclusion may limit the generalisability of the findings, although a small number of individuals did have a viral load >500,000 copies/mL at the baseline visit. The proportion of people with viral loads >500,000 copies/mL in recent clinical trials is generally small. For example, in the ADVANCE study [REF] where participants had relatively advanced HIV with a median CD4 count <350 cells/mm^3 in all arms,

Commented [LW90]: NAMSAL
Calmy A, Tovar Sanchez T, Kouanfack C et al; New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 Study Group. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. Lancet HIV. 2020 Oct;7(10):e677-e687.

Commented [LW91]: 1490: Sax PE, DeJesus E, Crofoot Get al. Coformulated bictegravir, emtricitabine, tenofovir alafenamide after initial treatment with bictegravir or dolutegravir and emtricitabine/tenofovir alafenamide. AIDS. 2018 Jul 31;32(12):1723-1725.

1489: Gallant J, Lazzarin A, Mills A et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017 Nov 4;390(10107):2063-2072.

Commented [LW92]: GEMINI - Cahn P, dero JS, Arribas JR et al. Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials. J Acquir Immune Defic Syndr. 2020 Mar 1;83(3):310-318.

Commented [LW93]: ADVANCE
Venter WDF, Moorhouse M, Sokhela S et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019 Aug 29;381(9):803-815.

the proportion with a baseline viral load above 500,000 copies/mL was 2–3% compared with 2% in the GEMINI studies [REF].

Commented [LW94]: GEMINI – as above

Drug-related adverse events in the pooled analysis were numerically more common in the three-drug regimen arm (24% *vs* 18%). However, there were few discontinuations due to adverse events with similar numbers between the two arms. As expected, differences in renal and bone turnover biomarkers were observed, consistent with the known effects of tenofovir-DF. The clinical significance of these changes is uncertain. Confirmed virological failure was rare and no treatment-emergent resistance mutations were seen in either arm at week 96.

While treatment failures in those with a CD4 count <200 cells/mm^3 were largely for reasons unrelated to study drug efficacy, the lack of clear evidence to support the use of this combination in this setting warrants caution when other regimens are available REF].

Commented [LW95]: GEMINI as above

In summary, dolutegravir/lamivudine recommended as initial treatment for most people living with HIV with the following caveats:

- It is **not** suitable for those with pre-treatment viral load >500,000 copies/mL;
- It is **not** suitable for those with a CD4 count <200 cells/mm^3;
- It is **not** suitable for those with hepatitis B co- infection;
- It is **not** suitable in the context of transmitted drug resistance (TDR);
- It is **not** suitable for those with documented/archived/suspected M184IV mutation;
- It is **not** suitable for those with HIV-related cognitive impairment;
- It is **not** suitable for those diagnosed during pregnancy;
- It should be considered with caution in specific populations such as those with PHI, opportunistic diseases or renal impairment.

5.3 Regimens recommended in certain clinical situations

5.3.1 Doravirine

Doravirine has been evaluated with a two-NRTI backbone in two large randomised controlled trials:

- DRIVE-AHEAD: a double-blind, non-inferiority trial comparing the fixed-dose combination of doravirine/lamivudine/tenofovir-DF with efavirenz/emtricitabine/tenofovir-DF, both given once daily [REF];

Commented [LW96]: DRIVE-AHEAD
Orkin C, Squires KE, Molina JM et al; DRIVE-AHEAD Study Group. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis. 2019 Feb 1;68(4):535-544.

- DRIVE-FORWARD: a double-blind, non-inferiority trial comparing once-daily doravirine with once-daily darunavir/ritonavir, both given with investigator-selected tenofovir-DF/emtricitabine (87%) or abacavir/lamivudine (13%) [REF].

Commented [LW97]: DRIVE-FORWARD
Molina JM, Squires K, Sax PE et al; DRIVE-FORWARD trial group. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. Lancet HIV. 2020 Jan;7(1):e16-e26.

In the comparison with efavirenz-based treatment, non-inferiority was demonstrated at week 48. The comparison was similar on all critical outcomes, other than for adverse events. There were generally fewer adverse events with doravirine; in the GRADE analysis there were significantly fewer discontinuations for adverse events in the doravirine arm (odds ratio [OR] 0.44, 95% CI 0.21–0.92). This difference was mainly due to well-recognised neuropsychiatric side effects of efavirenz. There were no changes in these comparisons from week 48 to week 96.

In the comparison with darunavir/ritonavir, non-inferiority was demonstrated at week 48. In this analysis, the viral suppression and discontinuation for adverse events favoured the doravirine arm at week 96. A Kaplan–Meier analysis showed a greater risk over time of discontinuation of darunavir due to adverse events. The expected side effect and toxicity profile was seen with darunavir, i.e. gastrointestinal symptoms and lipid adverse effects.

The rationale for recommending doravirine-based ART only for certain clinical scenarios is the current lack of comparison with INSTIs. Doravirine has shown broadly similar outcomes to efavirenz and boosted darunavir, whereas recommended INSTIs have shown superior outcomes to these agents. There is limited experience with abacavir/lamivudine with doravirine and therefore this NRTI backbone is not recommended in first-line treatment.

5.3.2 Raltegravir

SPRING-2 [REF] was a double-blind randomised controlled trial of tenofovir-DF/emtricitabine or abacavir/lamivudine plus raltegravir versus tenofovir-DF/emtricitabine or abacavir/lamivudine plus dolutegravir. In SPRING-2, dolutegravir was non-inferior to raltegravir at weeks 48 and 96 in terms of virological success [REF]. 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).

Commented [LW98]: SPRING-2
Raffi F, Jaeger H, Quiros-Roldan E et al; extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013 Nov;13(11):927-35.

Commented [LW99]: SPRING-2 – as above

SPRING-2 was not powered for a stratified viral load comparison but our analysis of the data showed a trend towards less virological failure on dolutegravir (OR 0.63, 95% CI 0.35–1.12) which was statistically significant at week 96 (OR 0.48, 95% CI 0.28–0.82). We were unable to analyse virological failure by baseline viral load

as these data were not available. There was a trend towards less virological failure with resistance on dolutegravir but confidence intervals were wide (at week 48: OR 0.13, 95% CI 0.01–2.61; at week 96: OR 0.13, 95% CI 0.01–2.47). Other critical outcomes were similar between raltegravir and dolutegravir.

In summary, raltegravir is recommended only in certain clinical scenarios based on the underperformance in terms of virological success for raltegravir compared to dolutegravir among people with a baseline viral load >100,000 copies/mL and the higher risk of virological failure at week 96, along with a numerically higher risk of resistance development which related to its demonstrably low genetic barrier [REF].

Commented [CNS100]: SWITCHMRK
Eron JJ, Young B, Cooper DA *et al.* Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet* 2010; **375**: 396–407.

5.3.3 Darunavir/ritonavir

In the randomised open-label Phase 3b FLAMINGO study, darunavir/ritonavir was compared with dolutegravir given in combination with investigator-selected tenofovir-DF/emtricitabine or abacavir/lamivudine [REF].

Commented [LW101]: FLAMINGO – as above

Dolutegravir demonstrated superior overall efficacy compared with darunavir/ritonavir in FLAMINGO (OR for success at 48 weeks 1.08, 95% CI 1.01–1.17; *P*=0.03) [17]. Superiority for virological success was maintained at week 96 (OR 1.92, 95% CI 1.27–2.91). The superior outcome related to a combination of fewer overall discontinuations and fewer discontinuations related to adverse events, however there was no difference in rates of virological failure and no instance of drug resistance in either arm. There were fewer discontinuations because of adverse events in those taking dolutegravir (1% *vs* 4%) though this did not reach statistical significance in our analysis. No differences were detected for other critical outcomes, although there were significantly more clinically serious adverse events in the dolutegravir arm (OR 2.00, 95% CI 1.05–3.80; *P*=0.03), but no difference in those deemed to be drug related.

For the comparison between darunavir/ritonavir 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 people with an undetectable HIV RNA at 96 weeks by intention-to-treat analysis was 88.3% for atazanavir/ritonavir, 93.9% for raltegravir and 89.4% for darunavir/ritonavir. Although a higher proportion of people experienced virological failure on darunavir/ritonavir (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/ritonavir 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/ritonavir arm: OR 0.24, 95% CI 0.11–0.52); however, there were no significant differences for the critical outcomes of grade 3/4 clinical or laboratory adverse events, headache and diarrhoea.

In summary, darunavir/ritonavir was inferior to dolutegravir in FLAMINGO, inferior to raltegravir in ACTG 5257, has a high propensity for drug–drug interactions and was associated with a higher risk of CVD in one cohort study, although this has not been observed in other studies [REFS]. Based in this, boosted darunavir is only recommended in certain clinical scenarios, such as TDR, same-day ART initiation or high risk of suboptimal adherence where a higher barrier to resistance is desired.

Commented [CNS102]: ANRS CO4 FHDH, Is the Risk of Myocardial Infarction in People With Human Immunodeficiency Virus (HIV) Associated With Atazanavir or Darunavir? A Nested Case-Control Study Within the French Hospital Database on HIV, *The Journal of Infectious Diseases*, Volume 221, Issue 4, 15 February 2020, Pages 516–522, Opsomer, et al.
Evaluation of cardiovascular disease risk in HIV-1-infected patients treated with Darunavir
.Drugs 2018; 18:199–210
Cardiovascular adverse events during treatment with darunavir-based regimens in an Italian observational study
Drug Des Devel Ther 2019; 13:1667–85

5.3.4 Atazanavir/ritonavir

ARIA was a randomised, open-label, Phase 3b non-inferiority study comparing atazanavir/ritonavir with dolutegravir conducted in women only [REF]. Dolutegravir was administered as a fixed-dose combination with abacavir/lamivudine, while the protease inhibitor (PI) was given with tenofovir-DF/emtricitabine. This study demonstrated superiority of dolutegravir/abacavir/lamivudine with viral load <50 copies/mL at week 48 demonstrated in 82% of participants taking the dolutegravir-based regimen versus 71% taking atazanavir/ritonavir (mean difference 10.5%, 95% CI 3.1–17.8; *P*=0.005). This difference was mainly driven by lower rates of adverse event-related discontinuation (4% *vs* 7%) and virological non-response in the dolutegravir arm (16 *vs* 35 events, OR 0.42, 95% CI 0.22–0.78). In our analysis, there were significantly fewer grade 3/4 events in those taking dolutegravir.

Commented [LW103]: ARIA - Orrell C, Hagins DP, Belonosova E et al; ARIA study team. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV. 2017 Dec;4(12):e536-e546.

Given the higher rates of virological failure and grade 3/4 adverse events along with the lower virological success, the use of atazanavir/ritonavir can be considered only in those where a boosted PI is required and who cannot take darunavir/ritonavir.

5.3.5 Tenofovir-DF/emtricitabine compared with tenofovir-AF/emtricitabine

In this analysis we considered Phase 3 randomised clinical trials. Two of the studies compared tenofovir-DF/emtricitabine with tenofovir-AF/emtricitabine in combination with elvitegravir/cobicistat, and one compared tenofovir-DF/emtricitabine with tenofovir-AF/emtricitabine in combination with darunavir/cobicistat; all three were double-blind trials [REF]. The open-label ADVANCE study also included a comparison of tenofovir-DF with tenofovir-AF. However, efavirenz was given with tenofovir-DF only, meaning that adverse events in particular were significantly affected by the efavirenz component. As a result, ADVANCE was excluded from the GRADE analysis.

Commented [LW104]: AMBER: Eron JJ, Orkin C, Gallant J et al; AMBER study group. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. AIDS. 2018 Jul 17;32(11):1431-1442.
Sax PE, Wohl D, Yin MT et al; GS-US-292-0104/0111 Study Team. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015 Jun 27;385(9987):2606-15.

In the GRADE analysis, a significant difference was seen only for the outcome of discontinuation for adverse events at week 48 (OR 1.97, 95% CI 1.08–3.59). In the trials in which elvitegravir/cobicistat was the third agent, discontinuation due to adverse events considered to be related to the study drug were very similar (tenofovir-AF *vs* tenofovir-DF: 7 [0.8%] *vs* 11 [1.3%] at week 48). However, a small number of participants

discontinued tenofovir-DF because of renal and bone events (four participants at week 48 and a further four at week 96) compared with none taking tenofovir-AF. In the study in which darunavir/cobicistat was used as the third agent, adverse event-driven discontinuation was seen in 2% of those taking tenofovir-AF versus 4% of those taking tenofovir-DF at week 48. Renal adverse events were more common in those taking tenofovir-DF (2% *vs* 6%) but none resulted in study drug discontinuation.

Decreases in bone mineral density (BMD), increases in markers of renal tubular dysfunction and changes in estimated glomerular filtration rate (eGFR) are generally seen in all these trials, favouring tenofovir-AF. These changes are small and of uncertain clinical significance for the majority of people living with HIV. A meta-analysis by [REF], which included trials including people treated for hepatitis B, suggested that these differences in renal and bone markers are not seen in the absence of the pharmacokinetic boosters cobicistat and ritonavir. It is noteworthy that boosters have been used in all the trials investigating initial treatment with either tenofovir-AF or tenofovir-DX.

Randomised trial data comparing continued tenofovir-DF with switch to tenofovir-AF/emtricitabine/elvitegravir/cobicistat showed greater improvement in renal biomarkers in people at higher risk of chronic kidney disease (CKD) than those at lower risk [REF] but a lack of data as to whether the same applies to first-line ART.

In conclusion, these differences between tenofovir-AF and tenofovir-DX are likely to have more clinical importance in people with established bone and/or renal disease, or in those with risk factors for these conditions where there is a desire to remove the risk of further drug-related deterioration.

5.3.6 Lamivudine versus emtricitabine in combination with tenofovir-DX

The 2015 BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy [REF] recommended tenofovir-DF/emtricitabine rather than tenofovir-DF/lamivudine due to a lack of clear evidence and in the absence of tenofovir-DF/lamivudine-containing fixed-dose combination. In addition, the longer intracellular half-life [REF], more efficient incorporation into proviral DNA [REF] and greater *in vitro* potency [REF] of emtricitabine provided biological plausibility for this agent being preferred.

Since then, however:

- WHO [REF], DHHS [REF] and EACS [REF] guidelines recommend lamivudine and emtricitabine as interchangeable, where applicable;

Commented [CNS105]: Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? J Virus Erad. 2018 Apr 1;4(2):72-79.

Commented [LW106]: DeJesus E, Haas B, Segal-Maurer S, Ramgopal MN, Mills A, Margot N, Liu YP, Makadzange T, McCallister S. Superior Efficacy and Improved Renal and Bone Safety After Switching from a Tenofovir Disoproxil Fumarate- to a Tenofovir Alafenamide-Based Regimen Through 96 Weeks of Treatment. AIDS Res Hum Retroviruses. 2018 Apr;34(4):337-342.

Commented [CNS107]: BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy

Commented [LW108]: Wang LH, Begley J, St Claire RL, 3rd *et al.* Pharmacokinetic and pharmacodynamic characteristics of emtricitabine support its once daily dosing for the treatment of HIV infection. *AIDS Res Hum Retroviruses* 2004; **20**: 1173–1182.

Commented [LW109]: Feng JY, Shi J, Schinazi RF, Anderson KS. Mechanistic studies show that (-)-FTC-TP is a better inhibitor of HIV-1 reverse transcriptase than 3TC-TP. *FASEB J* 1999; **13**: 1511–1517.

Commented [LW110]: Drogan D, Rauch P, Hoffmann D *et al.* The antiretroviral potency of emtricitabine is approximately 3-fold higher compared to lamivudine in dual human immunodeficiency virus type 1 infection/competition experiments in vitro. *Antiviral Res* 2010; **86**: 312–315.

Commented [LW111]: Panel on Antiretroviral Guidelines for Adults and Adolescents Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. 2020. https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf Available at: Last accessed April 2022

Commented [LW112]: DHHS ART guidelines – as above

Commented [LW113]: EACS guidelines https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf accessed 30 April 2022

- A review of three randomised controlled trials directly comparing the safety and efficacy of lamivudine versus emtricitabine concluded that the two drugs are therapeutically interchangeable [REF];
- An ATHENA cohort analysis showed no difference between lamivudine and emtricitabine in terms of virological response on PI-based ART over 5 years [REF] and although emtricitabine was associated with better virological outcomes with first-generation non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART in the same cohort [REF] this has not been replicated in trials of doravirine [REFS].

Of note, lamivudine may confer some advantages over emtricitabine for some people in terms of tolerability [REF], hyperpigmentation [REF] and mitochondrial toxicity [REF].

Fixed-dose combinations may limit choice; tenofovir-AF-based products are available only in combination with emtricitabine, and the fixed-dose combination for doravirine is based on tenofovir-DF/lamivudine.

In conclusion, where clinically appropriate and feasible, lamivudine and emtricitabine can be considered interchangeable.

5.4 Regimens not recommended first line compared to 2015 guidelines

5.4.1 Abacavir/lamivudine other than in combination with dolutegravir

Abacavir/lamivudine is associated with higher rates of virological failure compared to tenofovir-DF/emtricitabine with efavirenz or atazanavir/ritonavir [REF], and is associated with a higher risk of CVD [REF]; most modern studies have used tenofovir-based backbones.

5.4.2. Atazanavir/ritonavir

Ritonavir-boosted atazanavir was inferior to raltegravir for the combined endpoint in ACTG 5257, with a higher risk of adverse event-driven discontinuation in the same study [REF]. Atazanavir/ritonavir was also inferior to tenofovir-DF/emtricitabine/elvitegravir/cobicistat in WAVES [REF], inferior to dolutegravir in ARIA [REF] and associated with a higher risk of emergent CKD in D:A:D [REF]. In addition, boosted ART is associated with a high risk of drug–drug interactions [REF].

Commented [LW114]: Ford N, Vitoria M, Doherty M, Gray A. Candidates for inclusion in a universal antiretroviral regimen: are lamivudine and emtricitabine interchangeable? Curr Opin HIV AIDS. 2017 Jul;12(4):334-338.

Commented [LW115]: Rokx C, Gras L, van de Vijver D, Verbon A, Rijnders B; ATHENA National Observational Cohort Study. Virological responses to lamivudine or emtricitabine when combined with tenofovir and a protease inhibitor in treatment-naïve HIV-1-infected patients in the Dutch AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. HIV Med. 2016 Sep;17(8):571-80.

Commented [LW116]: Rokx C, Fibriani A, van de Vijver D, Verbon A, Schutten M, Gras L, Rijnders BJ. More virological failure with lamivudine than emtricitabine in efavirenz and nevirapine regimens in the Dutch nationwide HIV Cohort. J Int AIDS Soc. 2014 Nov 2;17(4 Suppl 3):19491.

Commented [LW117]: Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, Lai MT, Xu X, Rodgers A, Lupinacci L, Kumar S, Sklar P, Nguyen BY, Hanna GJ, Hwang C; DRIVE-FORWARD Study Group. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV. 2018 May;5(5):e211-e220. +

Commented [LW118]: Pollock K., Stebbing J., Bower M. Emtricitabine intolerance in treatment-experienced

Commented [LW119]: Borra's-Blasco J., Navarro-Ruiz A., Borra's C. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human

Commented [LW120]: Venhoff N., Stezer B., Melkaoiu K. Mitochondrial toxicity of tenofovir, emtricitabine and abacavir alone and in combination with additional

Commented [LW121]: ACTG 5202
Sax PE, Tierney C, Collier AC, et al; AIDS Clinical Trials Group Study A5202 Team. Abacavir/lamivudine versus tenofovir

Commented [LW122]: Sabin CA, Ryom L, d'Arminio Monforte A et al; D:A:D Study Group. Abacavir use and risk

Commented [LW123]: ACTG 5257
Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase

Commented [LW124]: WAVES
Squires K, Kityo C, Hodder S et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected wome

Commented [LW125]: ARIA – as above

Commented [LW126]: DAD CKD
Ryom L, Mocroft A, Kirk O et al; D:A:D Study Group. Association between antiretroviral exposure and renal

Commented [CNS127]: Reyataz Summary of Product Characteristics.

5.4.3 Efavirenz

Efavirenz was inferior to dolutegravir in SINGLE [REF], with higher rates of suicidality [REFS] and more adverse events and adverse event-driven discontinuations than other recommended agents [REFS].

5.4.4 Rilpivirine

Rilpivirine is non-inferior to efavirenz first line with lower rates of toxicity [REFS] but higher risk of resistance emergence at virological failure; food requirement and interaction with acid-reducing agents are considerations.

5.4.5 Elvitegravir/cobicistat

Cobicistat-boosted elvitegravir is non-inferior to efavirenz [REF] and atazanavir/ritonavir [REF] and superior to atazanavir/ritonavir in women [REF]. Complexity of drug–drug interactions with relatively high risk of resistance emergence at virological failure are considerations [REFS].

5.5 What to start in the context of TDR

Recommendations

- Standard genotypic resistance testing (of reverse transcriptase and protease) is recommended in ART-naïve individuals (GPP).
- Baseline integrase resistance testing should be considered in addition (GPP) if:
- Any major mutations to other drug classes are detected *or*
- If diagnosis is made in pregnancy *or*
- If there are other reasons to suspect transmitted integrase resistance (e.g. likely acquisition from a source with suspected or known integrase resistance).
- We recommend that ART-naïve people living with HIV and evidence of TDR should start ART containing tenofovir-DX or tenofovir-AF with lamivudine or emtricitabine plus one of the following: dolutegravir, bictegravir or boosted darunavir (GPP).

Rationale

Transmission of drug-resistant HIV has historically been associated with suboptimal virological responses to ART [REFS]. Genotypic resistance testing is therefore recommended prior to starting ART, ideally at the time of HIV diagnosis. The BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals recommend genotypic sequencing of the reverse transcriptase and protease genes but not, at

Commented [LW128]: SINGLE – as above

Commented [LW129]: ACTG + START
As per ACTG ref in mental health section

Commented [LW130]: SINGLE as before
STARTMRK: Rockstroh JK, Lennox JL, Dejesus E et al; STARTMRK Investigators. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. Clin Infect Dis. 2011 Oct;53(8):807-16. doi: 10.1093/cid/cir510. PMID: 21921224.
DRIVE-AHEAD as before
Gatell JM, Morales-Ramirez JO, Hagins DP, Thompson M, Keikawus A, Hoffmann C, Rugina S, Osiyemi O, Escoriu S, Dretler R, Harvey C, Xu X, Teppler H. Forty-eight-week efficacy and safety and early CNS tolerability of doravirine (MK-1439), a novel NNRTI, with TDF/FTC in ART-naive HIV-positive patients. J Int AIDS Soc. 2014 Nov 2;17(4 Suppl 3):19532.
(i.e. 4 refs)

Commented [LW131]: Cohen CJ, Molina JM, Cassetti I et al; ECHO, THRIVE study groups. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. AIDS. 2013 Mar 27;27(6):939-950.
van Lunzen J, Antinori A, Cohen CJ, Arribas JR, Wohl DA, Rieger A, Rachlis A, Bloch M, Segal-Maurer S, Garner W, Porter D, Bosse M, Piontkowsky D, Chuck SK, De-Oertel S. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. AIDS. 2016 Jan;30(2):251-9.

Commented [LW132]: Choi JY, Sungkanuparph S, Anekthananon T et al. Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in Asian Subjects with Human Immunodeficiency Virus 1 Infection: A Sub-Analysis of Phase 3 Clinical Trials. Infect Chemother. 2016 Sep;48(3):219-224.

Commented [LW133]: WAVES; as before

Commented [LW134]: CHoi: as above

Commented [LW135]: Phanuphak P, Sirivichayakul S, Jiamsakul A et al. Transmitted drug resistance and antiretroviral treatment outcomes in non-subtype B HIV-1-infected patients in South East Asia. J Acquir Immune Defic Syndr. 2014 May 1;66(1):74–79.

the time of writing, the integrase gene [REF]. If transmitted integrase resistance is a concern, for example where there is major drug resistance to other classes of ARV agents, then sequencing of the integrase gene should also be considered at baseline.

The rationale for these recommendations comes from the TDR prevalence in 2016 in the UK [REF]. Of 3182 baseline tests, 9.6% had at least one mutation; 4.2%, 4.1% and 2.2% of samples had at least one mutation that conferred resistance to NRTI (mainly single thymidine analogue mutations), NNRTI (most commonly K103N [2.7%] and G190A [0.5%]) and PI (most commonly L90M [0.8%] and M46L [0.5%[) respectively. Baseline integrase sequencing is performed infrequently in routine clinical practice in the UK, but informative data come from a study of 655 individuals with recently acquired HIV between 2014 and 2016 [REF]. Using ultradeep sequencing, no major integrase resistance mutations were identified at high variant frequency (>20%), although a few low-frequency variants of doubtful clinical significance were observed [REF]. The transmission of multidrug-resistant HIV variants is rare and resistance testing alongside expert opinion can guide treatment choices in such cases.

There are no published prospective clinical trials comparing different ART regimens in the presence of TDR. Thus, recommendations are based on extrapolation from other clinical studies. It was previously considered that thymidine analogue mutations reduced tenofovir-DF sensitivity, but accumulating evidence from trials of second-line therapy demonstrate that the use of tenofovir-DF as part of a second-line regimen is highly effective even in the presence of multiple thymidine analogue mutations acquired during first-line ART [REFS]. The M184V/I mutation, which confers high-level resistance to emtricitabine/lamivudine, is rarely detected in baseline resistance samples. Where the M184V/I mutation is present (in the absence of compensatory mutations) [REF], their high fitness cost results in their rapid disappearance to undetectable levels [REF].

The second-generation INSTIs dolutegravir and bictegravir have a high genetic barrier to resistance when compared to raltegravir and elvitegravir [REFS]. Treatment-emergent resistance has been reported very rarely in individuals receiving dolutegravir- or bictegravir-based initial therapy [REFS]. As noted above, transmitted integrase resistance was rare in 2014–2016 but as the use of INSTIs has increased since that time ongoing surveillance and updated analysis of the prevalence of INSTI TDR is warranted.

Similarly, boosted darunavir has a high genetic barrier to resistance and a low rate of treatment-emergent resistance. Darunavir-based therapy, in combination with NRTIs, was non-inferior to dolutegravir-based ART when used as second-line treatment in patients with extensive resistance following virological failure with an NNRTI-based initial regimen [REF].

Commented [CNS136]: BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals 2016 (2019 interim update)

Commented [WLJ(ANWLN137]: UKHIV Drug Resistance Database: http://www.hivrdb.org.uk/hiv-drug-resistance-uk

Commented [WLJ(ANWLN138]: **Mbisa JL, Ledesma J, Kirwan P et al. Surveillance of HIV-1 transmitted integrase strand transfer inhibitor resistance in the UK. J Antimicrob Chemother. 2020 Nov 1;75(11):3311-3318. doi: 10.1093/jac/dkaa309.**

Commented [WLJ(ANWLN139]: EARNEST: Hakim JG, Thompson J, Kityo C et al; Europe Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial Team. Lopinavir plus nucleoside reverse-transcriptase inhibitors, lopinavir plus raltegravir, or lopinavir monotherapy for second-line treatment of HIV (EARNEST): 144-week follow-up results from a randomised controlled trial. Lancet Infect Dis. 2018 Jan;18(1):47-57.
SECOND LINE: SECOND-LINE Study Group, Boyd MA, Kumarasamy N, Moore CL et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. Lancet. 2013 Jun 15;381(9883):2091-9.
DAWNING: Aboud M, Kaplan R, Lombaard J et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. Lancet Infect Dis. 2019 Mar;19(3):253-264.
NADIA: Paton NI, Musaazi J, Kityo C et al; NADIA Trial Team. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022 Apr 20:S2352-3018(22)00092-3.

Commented [CNS140]: Gregson J, Rhee SY, Datir R et al. Human Immunodeficiency Virus-1 Viral Load Is Elevated in Individuals With Reverse-Transcriptase Mutation M184V/I During Virological Failure of First-Line Antiretroviral Therapy and Is Associated With Compensatory Mutation L74I. J Infect Dis. 2020 Sep 1;222(7):1108-1116.

Commented [CNS141]: INSIGHT ref as above

Commented [WLJ(ANWLN142]: SINGLE, SPRING, FLAMINGO, etc, GS 1489 and 1490 – all as referenced earlier in text

Commented [WLJ(ANWLN143]: Fulcher JA, Du Y, Zhang TH, Sun R, Landovitz RJ. Emergence of Integrase Resistance Mutations During Initial Therapy Containing Dolutegravir. Clin Infect Dis. 2018 Aug 16;67(5):791-794. ...

Commented [WLJ(ANWLN144]: NADIA - As above

The lower barrier to development of resistance in the NNRTI class means that an NNRTI-based regimen is not recommended where NRTI or NNRTI TDR is detected.

The evolution of treatment guidelines towards regimens that include two NRTIs and a third agent with a high genetic barrier as first-line ART means that such regimens are likely to be highly active in patients with TDR.

It is therefore recommended that for initiation of therapy for people living with HIV in the presence of TDR, the following regimens should be considered:

- Dolutegravir + tenofovir-DF/tenofovir-AF + emtricitabine/lamivudine
- Boosted darunavir + tenofovir-DF/tenofovir-AF + emtricitabine/lamivudine
- Bictegravir/tenofovir-AF/emtricitabine

We do not recommend dolutegravir/lamivudine as initial therapy where there is TDR.

5.6 What to start in the context of rapid ART initiation

Where rapid ART is indicated or preferred, we advise a cautious approach by recommending the same regimens as for first-line therapy in the context of TDR (see Section 5.5 What to start in the context of TDR):

1. Dolutegravir + tenofovir-DF/tenofovir-AF + emtricitabine/lamivudine or bictegravir/tenofovir-AF/emtricitabine
2. Boosted darunavir + tenofovir-DF/tenofovir-AF + emtricitabine/lamivudine

There is a paucity of data investigating optimal initial regimens for rapid ART; two single-arm studies conducted in the US have been published. The DIAMOND study investigated darunavir/cobicistat/emtricitabine/tenofovir-AF as an initial regimen within 14 days of diagnosis without baseline results [REF]. At week 48, 89% of the 109 participants had a viral load less than 50 copies/mL and none needed to change ART once baseline resistance tests were available. There were no protocol-defined virological failures, no serious adverse events, one adverse event-driven discontinuation and high treatment satisfaction scores. The STAT study investigated dolutegravir/lamivudine in a test-and-treat strategy for newly diagnosed individuals [REF], also within 14 days of diagnosis without access to baseline results. Treatment modification was necessary for eight of 131 participants (6%): five due to hepatitis B coinfection and one case of baseline M184V, one case of rash and one due to participant choice. At week 24, 78% of all participants and 92% of the 111 with available data achieved a viral load less than 50 copies/mL. Currently there are no published data on the use of bictegravir/tenofovir-AF/emtricitabine in this setting but based on

Commented [WLJ(ANWLN145]: Huhn GD, Crofoot G, Ramgopal M, Gathe J, Bolan R, Luo D, Simonson RB, Nettles RE, Benson C, Dunn K. Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in a Rapid-Initiation Model of Care for Human Immunodeficiency Virus Type 1 Infection: Primary Analysis of the DIAMOND Study. Clin Infect Dis. 2020 Dec 15;71(12):3110-3117..

Commented [WLJ(ANWLN146]: Rolle CP, Berhe M, Singh T, Ortiz R, Wurapa A, Ramgopal M, Leone PA, Matthews JE, Dalessandro M, Underwood MR, Angelis K, Wynne BR, Merrill D, Nguyen C, van Wyk J, Zolopa AR. Dolutegravir/lamivudine as a first-line regimen in a test-and-treat setting for newly diagnosed people living with HIV. AIDS. 2021 Oct 1;35(12):1957-1965.

the head-to-head comparisons with dolutegravir-based ART outlined above, this regimen is also recommended for rapid ART.

INSTIs yield more rapid viral suppression (although only dolutegravir has been compared with boosted darunavir first line [REF]) and demonstrate a better tolerability profile.

It is important that when full baseline assessment has been undertaken, ART should be reviewed in line with these guidelines and, where appropriate, other prescribing policies.

5.7 What to start in the context of very high viral load

Recommendations

- We suggest that three-drug ART combinations characterised by a high barrier to resistance are initiated or re-initiated in people with very high viral loads (>500,000 copies/mL) (Grade 2B).
- We suggest tenofovir-DX or tenofovir-AF plus lamivudine or emtricitabine plus dolutegravir or bictegravir or boosted darunavir are used (GPP).

Rationale

The goal of ART in individuals presenting with a very high viral load is to suppress plasma HIV RNA to undetectable levels to minimise the risk of disease progression as soon as possible and realise the benefits in terms of preventing HIV transmission. Hence, individuals should be encouraged to initiate or re-initiate therapy as soon they are ready.

Clinical trial data regarding the treatment of HIV infection with very high viral load are limited. However, three-drug ART combinations characterised by a high barrier to resistance because they contain dolutegravir, bictegravir or boosted darunavir have been shown to lead to the achievement and maintenance of an undetectable viral load [REF]. A potential advantage of INSTI-based ART is more rapid viral suppression [REF] and a lower risk of drug–drug interaction [REF].

A cohort analysis from Switzerland demonstrated that a baseline viral load >100,000 copies/mL was associated with a higher risk of treatment failure among individuals commencing first-line INSTI-based ART [REF]. About two-thirds of people started dolutegravir-based ART (the study was undertaken before routine use of bictegravir) and among those with baseline viral load >100,000 copies/mL, dolutegravir was associated with faster viral suppression than raltegravir (*P*<0001).

Commented [LW147]: FLAMINGO: as before

Commented [CNS148]: Clotet B, Feinberg J, van Lunzen J *et al.* Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet* 2014; **383**: 2222–2231.

Commented [LW149]: Clotet et al. Lancet 2014 as above https://pubmed.ncbi.nlm.nih.gov/24698485/

Commented [LW150]: Liverpool University HIV Drug Interaction Checker https://www.hiv-druginteractions.org/ accessed 30 April 2022

Commented [LW151]: Pyngottu A, Scherrer AU, Kouyos R et al; Swiss HIV Cohort Study. Predictors of Virological Failure and Time to Viral Suppression of First-Line Integrase Inhibitor-Based Antiretroviral Treatment. Clin Infect Dis. 2021 Oct 5;73(7):e2134-e2141.

ART combinations containing more than three active drugs have not shown a benefit in terms of achievement and maintenance of viral load <50 copies/mL versus three-drug regimens, though none of the 12 studies in this meta-analysis specifically recruited participants with high baseline viral load [REF].

Commented [LW152]: Feng Q, Zhou A, Zou H et al. Quadruple versus triple combination antiretroviral therapies for treatment naive people with HIV: systematic review and meta-analysis of randomised controlled trials *BMJ* 2019; 366 :l4179

The importance of adherence in people starting or restarting ART with a high viral load needs to be underlined. As for all ART-naïve persons who are starting ART or for individuals who are restarting ART, the results of drug resistance testing should guide selection of the ART combination. However, ART can be initiated while awaiting confirmation of the resistance test result if deemed necessary (see Section 4.2 Same-day ART initiation).

5.8 What to start in people diagnosed with HIV on PrEP

Given the increasing use of tenofovir-DF/emtricitabine as PrEP, infection may be diagnosed in some individuals while they are taking tenofovir-DF/emtricitabine PrEP or after a period of suboptimal PrEP intake. Therefore, in this setting, drug resistance results are particularly important. The ART combinations listed for rapid ART are recommended options while awaiting resistance testing results.

5.9 Switching ART in virological suppression

Recommendations

- We recommend that most people should be on a regimen that is preferred for first-line therapy or considered acceptable for switch/maintenance (GPP).
- We recommend that, in individuals on suppressive ART regimens, consideration is given to differences in side effect profile, drug–drug interactions, dosing requirements and known/suspected drug resistance before switching any ART component (GPP).
- We recommend particular caution when switching from a high-genetic barrier to a low-genetic barrier regimen in the presence of known or suspected resistance (Grade 1B).
- When switching from an NNRTI there may be pharmacological considerations (see Section 6.2 Pharmacology) (GPP).
- In individuals with previous NRTI resistance mutations, we recommend against switching a boosted PI to an NNRTI or first-generation INSTI as the core agent (Grade 1B).
- In individuals with any NNRTI resistance, we recommend not switching to NNRTI-based ART (GPP).
- We recommend review of ART at least annually (GPP).

- Where an individual is on a non-recommended regimen, we recommend regular review and clear documentation of rationale (GPP).
- Abacavir should only be considered for people who are HLA B*5701 negative (Grade 1A).
- Due to associations with long-term toxicity and potential harm of drug–drug interactions, switching from a PI to an INSTI or NNRTI is advised where clinically appropriate (GPP).

Auditable outcome

- Proportion of individuals with documented previous NRTI resistance who have remained suppressed after switching ART.

Rationale

In individuals on fully virally suppressive regimens, switching components of the ART combination may be considered for several reasons, including: management of ARV drug toxicity or intolerance, more convenient dosing, to reduce pill burden, management of potential drug–drug interactions, individual preference and cost [REF]. 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 Pharmacology.

Commented [CNS153]: 1. Arribas JR, Delgado R, Arranz A et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. J Acquir Immune Defic Syndr 2009; 51: 147–152.

Switching ART should not be at the cost of virological efficacy. The following summarises the key principles of switching ART and which regimens are considered acceptable for switching or continuing in people already stable on those regimens. Of note, all options recommended for first-line ART are also suitable for use in the context of suppressed switch if considered clinically appropriate and acceptable to the individual concerned.

5.10 Suppressed switch or maintenance

All regimens recommended for first-line ART are also recommended for suppressed switch or maintenance. In addition, the following regimens are also acceptable (see Table 5.2).

Table 5.2 Recommendations for choice of ART for suppressed switch or maintenance

Acceptable for switch or to continue where clinically appropriate ***Where feasible, lamivudine and emtricitabine are considered interchangeable***
NNRTI-based three-drug regimens

Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine plus doravirine	
Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine plus rilpivirine	
Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine plus efavirenz	Maintenance only; not recommended routinely for switch due to risk of neuropsychiatric toxicity, unless considered most clinically appropriate option
Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine plus nevirapine	Maintenance only; not recommended routinely for switch due to small risk of severe toxicity
INSTI-based three-drug regimens	
Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine with dolutegravir	
Tenofovir-AF/emtricitabine/bictegravir	
Tenofovir-DX/emtricitabine/elvitegravir/cobicistat or tenofovir-AF/ emtricitabine/elvitegravir/cobicistat	Improvements in renal/bone biomarkers for tenofovir-AF compared to tenofovir-DF are most evident in the context of boosted ART
PI-based regimens	
Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine with atazanavir/ritonavir or atazanavir/cobicistat	Where resistance necessitates a PI; improvements in renal/bone biomarkers for tenofovir-AF over tenofovir-DF are most evident in the context of boosted ART. Atazanavir and tenofovir-DX are both associated with renal toxicity
Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine with darunavir/ritonavir or darunavir/cobicistat	Where resistance necessitates a PI; improvements in renal/bone biomarkers for tenofovir-AF over tenofovir-DF are most evident in the context of boosted ART
Tenofovir-DX/emtricitabine or tenofovir-AF/ emtricitabine or abacavir/lamivudine with lopinavir/ritonavir	Where resistance necessitates a PI; improvements in renal/bone biomarkers for tenofovir-AF over tenofovir-DF are most evident in the context of boosted ART
Two-drug regimens	
Dolutegravir/lamivudine	

Dolutegravir/rilpivirine	Studied only in suppressed switch; high risk of NNRTI resistance at virological failure
Cabotegravir + rilpivirine injectable	Studied only in suppressed switch; high risk of NNRTI and INSTI resistance at virological failure
Raltegravir with darunavir/ritonavir or darunavir/cobicistat	Underperformed at viral load >100,000 copies/mL and CD4 <200 cells/mm^3 when used first line
Dolutegravir with darunavir/ritonavir or darunavir/cobicistat	Studied only in suppressed switch
Lamivudine or emtricitabine with darunavir/ritonavir or darunavir/cobicistat or atazanavir/ritonavir or atazanavir/cobicistat or lopinavir/ritonavir	In the absence of known or suspected M184V/I. Several studies demonstrate non-inferiority of lamivudine with a boosted PI. ATLAS-M demonstrated switch to lamivudine + atazanavir/ritonavir was superior to continuing tenofovir-DX/emtricitabine + atazanavir/ritonavir in people with viral suppression and no NRTI resistance
ARVs that may play a role in specific circumstances	
Though not recommended routinely, there are some agents that may be used based on a need to deliver ART parenterally or an inability to otherwise create a suppressive regimen: • Zidovudine • Etravirine • Maraviroc • Enfuvirtide • Fostemsavir • Ibalizumab	

5.10.1 NRTI switch

In the absence of NRTI resistance, abacavir/lamivudine, tenofovir-DX/lamivudine, tenofovir-DX/emtricitabine and tenofovir-AF/emtricitabine can all be expected to deliver similar virological efficacy. In people who have experienced virological failure, NRTI choice should be guided by resistance testing; there is evidence that tenofovir is more likely to retain activity than abacavir in this context because the M184V mutation reduces abacavir susceptibility but leads to tenofovir hypersusceptibility [REF].

Commented [LW154]: Derache A, Iwuji CC, Danaviah S, Giandhari J, Marcelin AG, Calvez V, de Oliveira T, Dabis F, Pillay D, Gupta RK. Predicted antiviral activity of tenofovir versus abacavir in combination with a cytosine analogue and the integrase inhibitor dolutegravir in HIV-1-infected South African patients initiating or failing first-line ART. J Antimicrob Chemother. 2019 Feb 1;74(2):473-479. doi: 10.1093/jac/dky428. PMID: 30380053; PMCID: PMC6337894.

In general, switching from tenofovir-DF to tenofovir-AF is associated with improvements in renal and bone biomarkers and slight worsening of lipid parameters. In the GS-109 study, 1436 people on one of four suppressive tenofovir-DF/emtricitabine-based regimens were randomly assigned to continue or switch to tenofovir-AF/emtricitabine/elvitegravir/cobicistat [REF]. In terms of baseline ART, 32% were on elvitegravir/cobicistat, 26% on efavirenz and 42% on boosted atazanvir (approximately two-thirds ritonavir-boosted and one-third cobicistat-boosted). Viral suppression at week 96 was significantly higher in the switch arm though as most individuals also switched third agent it is not possible to attribute this to the backbone switch and the difference was not driven by discontinuations for efficacy, adverse events or death. Three of six virological failures in the switch arm developed resistance compared to one of two virological failures in the continued ART arm. Hip and spine BMD remained stable or decreased in the continued ART arm and increased in the switch arm yielding a statistically significant difference at week 96, and a greater proportion of participants saw recovery from osteopenia or osteoporosis in the switch arm. It was difficult to interpret serum creatinine changes in this study as most people in the switch arm switched to cobicistat for the first time which is associated with a rise in serum creatinine due to inhibition of creatinine secretion in the proximal tubule [REF]. Excluding those on efavirenz (i.e. unboosted ART) at baseline, there was a small increase in eGFR in the switch group compared with minimal change on continued ART. Urine protein and albumin levels decreased in those who switched to tenofovir-AF, regardless of baseline ART, and increased in the continued ART group with a statistically significant difference favouring switch at week 96. Lipid results were difficult to interpret as efavirenz [REF] is associated with a more negative impact on lipids than elvitegravir/cobicistat but first-line trials have demonstrated an advantage of tenofovir-DF over tenofovir-AF in terms of lipid fractions [REF]. A single-arm study switching people with renal impairment (eGFR 30–69 mL/min) to tenofovir-AF/emtricitabine/elvitegravir/cobicistat demonstrated maintained viral suppression, stable eGFR and improvements in proteinuria, markers of proximal tubule function and hip and spine BMD [REF]. A cohort from the UK demonstrated significant improvement in eGFR slope in 357 patients who switched from tenofovir-DX- to tenofovir-AF-containing ARV regimens [REF].

Switching from tenofovir-DF, and to a lesser degree abacavir, to tenofovir-AF is associated with an increase in weight. In a pooled analysis of 12 prospective clinical trials, virally suppressed people who switched from tenofovir-DF or abacavir to tenofovir-AF experienced significant weight gain at week 48 (+1.6 kg for tenofovir-DF) [REF]. In addition, switching from tenofovir-DF to tenofovir-AF was associated with a significantly higher risk of experiencing ≥10% weight gain at week 48 (OR 2.58, 95% CI 1.94–3.43). Two other studies demonstrated ≥2 kg weight gain at week 48 for people switching to tenofovir-AF versus those staying on tenofovir-DF: the randomised controlled trial GS-4030 [REF] and the US OPERA cohort [REF]. Whether

Commented [LW155]: DeJesus E, Haas B, Segal-Maurer S, Ramgopal MN, Mills A, Margot N, Liu YP, Makadzange T, McCallister S. Superior Efficacy and Improved Renal and Bone Safety After Switching from a Tenofovir Disoproxil Fumarate- to a Tenofovir Alafenamide-Based Regimen Through 96 Weeks of Treatment. AIDS Res Hum Retroviruses. 2018 Apr;34(4):337-342..

Commented [LW156]: Tybost Summary of Product Characteristics https://www.medicines.org.uk/emc/product/1277/smpc#gref accessed 30 April 2022

Commented [LW157]: Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, Gallant JE, Liu HC, Zhong L, Yale K, White K, Kearney BP, Szwarcberg J, Quirk E, Cheng AK; GS-US-236-0102 study team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet. 2012 Jun 30;379(9835):2439-2448. 22748591.

Commented [LW158]: Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, Gallant JE, Liu HC, Zhong L, Yale K, White K, Kearney BP, Szwarcberg J, Quirk E, Cheng AK; GS-US-236-0102 study team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of ...

Commented [LW159]: Post FA, Tebas P, Clarke A, Cotte L, Short WR, Abram ME, Jiang S, Cheng A, Das M, Fordyce MW. Brief Report: Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Adults With Renal ...

Commented [LW160]: Ibrahim F, Campbell L, Bailey AC, et al. Estimated glomerular filtration rate slopes on tenofovir alafenamide. HIV Med. 2020 Oct;21(9):607-612.

Commented [CNS161]: Erlandson KM, Carter CC, Melbourne K, et al. Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials. Clin Infect Dis. 2021 Oct 20;73(8):1440-1451.

Commented [LW162]: Sax PE, Rockstroh JK, Luetkemeyer AF, Yazdanpanah Y, Ward D, Trottier B, Rieger A, Liu H, Acosta R, Collins SE, Brainard DM, Martin H; GS-US-380–4030 Investigators. Switching to Bictegravir, Emtricitabine, and Tenofovir Alafenamide ...

Commented [LW163]: Mallon PW, Brunet L, Hsu RK, Fusco JS, Mounzer KC, Prajapati G, Beyer AP, Wohlfeiler MB, Fusco GP. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. J Int AIDS Soc. 2021 Apr;24(4):e25702.

this is due to an effect of tenofovir-DF in limiting the weight gain, generally seen as people age, or a direct causal effect of tenofovir-AF is uncertain (see Section 8.3.3 Weight gain considerations).

Studies switching from a two-NRTI-based three-drug regimen to dolutegravir or boosted PI with one NRTI are summarised below.

5.10.2 PI switch

Most studies investigating switching within the PI class investigated now non-recommended or unboosted regimens. Due to the association with long-term toxicity [REFS] combined with the complexities and potential harm of drug–drug interactions secondary to ritonavir and cobicistat, switching from a PI to an INSTI or NNRTI is advised where clinically appropriate.

Careful attention should be paid to any likely or known resistance and particular caution is advised when switching to a low-barrier regimen as illustrated by the SWITCHMRK results [REF]. In the randomised SWITCHMRK study, switching to raltegravir with at least two NRTIs failed to show non-inferiority to continued PI-based ART in participants who may have experienced prior virological failure. The ODIS study yielded similar results [REF]; individuals suppressed on PI-based therapy with prior NRTI resistance experienced much higher rates of virological failure on switching to once- or twice-daily raltegravir than those with no NRTI resistance (16.2% *vs* 0.7%; *P*<0.001). By contrast, the SPIRAL study showed switching to raltegravir to be non-inferior to continued boosted PI with two NRTIs, with significant improvements in lipid parameters; the difference between the results from the SPIRAL, ODIS and SWITCHMRK studies may be explained by risk of NRTI resistance and duration of viral suppression prior to study entry. One randomised controlled trial assessed switching from a PI to cobicistat-boosted elvitegravir in people with viral suppression (excluding individuals with a history of virological failure or resistance to tenofovir-DF or emtricitabine) and found that suppression was maintained and the regimen was well tolerated [REF].

In STRATEGY-PI, virally suppressed people on a ritonavir-boosted PI with emtricitabine plus tenofovir-DF were randomly allocated to switch to coformulated tenofovir-DF/emtricitabine/elvitegravir/cobicistat or to continue on their existing regimen [REF]. Exclusion criteria included any history of virological failure, and all participants were required to have a pre-ART resistance test demonstrating an absence of NRTI mutations. Around 40% of participants were on atazanavir, 40% on darunavir and the remainder on older PIs; virological efficacy was proven, indeed the switch arm demonstrated statistically superior virological outcomes. Minor improvements in lipids were observed, most notable in those on lopinavir/ritonavir at baseline. Switching from a boosted-darunavir or boosted-atazanavir to tenofovir-AF/emtricitabine/bictegravir in virally suppressed, INSTI-naïve people with no documented resistance to abacavir, lamivudine, emtricitabine or

Commented [LW164]: Ryom L, Lundgren JD, El-Sadr Wet al; D:A:D study group. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV. 2018 Jun;5(6):e291-e300.
Ryom L, Dilling Lundgren J, Reiss P, et al; Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. Use of Contemporary Protease Inhibitors and Risk of Incident Chronic Kidney Disease in Persons With Human Immunodeficiency Virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. J Infect Dis. 2019 Oct 8;220(10):1629-1634.

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Commented [LW166]: Vispo E, Barreiro P, Maida I *et al.* Simplification from protease inhibitors to once- or twice-daily raltegravir: the ODIS trial. *HIV Clin Trials* 2010; **11**: 197–204.

Commented [LW167]: Fisher M, Nelson M, Johnson M *et al*. Simplification of PI+RTV+FTC/TDF to E/C/F/TDF maintains HIV suppression and is well tolerated. *HIV Med* 2014; **15 (Suppl 3)**: 114.

Commented [LW168]: Arribas JR, Pialoux G, Gathe J, Di Perri G, Reynes J, Tebas P, Nguyen T, Ebrahimi R, White K, Piontkowsky D. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. Lancet Infect Dis. 2014 Jul;14(7):581-9..

tenofovir was investigated in the randomised, open-label GS-1878 trial [REF]. Switching to bictegravir-based ART demonstrated non-inferior virological efficacy; lipid improvements were observed in those switching from abacavir-based ART but not those switching from tenofovir-DF, presumably because the benefit of switching off a boosted PI was balanced by the lipid increase when switching from tenofovir-DF to tenofovir-AF. There are limited data to support switching to tenofovir-AF/emtricitabine/bictegravir in the context of NRTI resistance [REF] but this is only in the context of viral suppression and studies have tended to combine known genotypic resistance with mutations detected on proviral sequencing which may not have the same clinical implications. By contrast, dolutegravir has been studied in people on failing first-line NNRTI-based ART and shown to be superior to lopinavir/ritonavir in DAWNING and non-inferior to darunavir/ritonavir in NADIA. A small proportion (about 8%) of people in the TANGO and SALSA trials (both investigating switch from a suppressive three-drug regimen to dolutegravir/lamivudine) were on a boosted PI at baseline, mainly darunavir, and demonstrated maintained efficacy. There are no published trials specifically investigating switching from a boosted PI to dolutegravir.

Previous treatment failure on an NRTI-containing regimen has also been associated with an increased risk of virological failure when switching from a PI- to an NNRTI-based regimen [REF]. One randomised controlled trial has assessed the switch from PI to once-daily etravirine in people with HIV RNA suppression [REF] and no participants presented with virological failure through to 48 weeks. In the SPIRIT Study, switching in virological suppression to rilpivirine from PI-maintained suppression was safe and, with or without K103N, had a high response rate. People on a suppressive boosted PI plus two-NRTI regimen were randomly assigned to continue current ART or switch to a fixed-dose combination of tenofovir-DF/ emtricitabine/rilpvirine [REF]. Importantly, participants were required to have a pre-ART resistance test demonstrating no mutations conferring resistance to study drugs; switching to the NNRTI regimen was non-inferior to continued boosted PI and yielded significant lipid improvements. The randomised DRIVE-SHIFT study investigated continued ART versus switching to doravirine/lamivudine/tenofovir-DF in people suppressed on ritonavir- or cobicistat-boosted PI (atazanavir, darunavir or lopinavir), cobicistat-boosted elvitegravir or an NNRTI (efavirenz, nevirapine or rilpivirine), each in combination with two NRTIs [REF]. Eligible participants were required to have been virally suppressed for at least 6 months with no history of virological failure and switching to doravirine was non-inferior to continued ART. For individuals without previous NRTI or NNRTI resistance mutations, switching from a boosted PI to any of the currently licensed NNRTIs is likely to maintain virological efficacy and choice of NNRTI will depend on side effect profile, tolerability and individual preference. For individuals with known NNRTI mutations that are not predicted to impact susceptibility to a given NNRTI there are insufficient data to make a recommendation. A total of 24 patients in the SPIRIT trial had a history of the K103N mutation and the majority maintained viral

Commented [LW169]: Daar ES, DeJesus E, Ruane P, Crofoot G, Oguchi G, Creticos C, Rockstroh JK, Molina JM, Koenig E, Liu YP, Custodio J, Andreatta K, Graham H, Cheng A, Martin H, Quirk E. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2018 Jul;5(7):e347-e356..

Commented [LW170]: Andreatta K, Willkom M, Martin R, Chang S, Wei L, Liu H, Liu YP, Graham H, Quirk E, Martin H, White KL. Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184V/I. J Antimicrob Chemother. 2019 Dec 1;74(12):3555-3564.

Commented [LW171]: Martinez E, Arnaiz JA, Podzamczer D *et al.* Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003; **349**: 1036–1046.

Commented [LW172]: Echeverria P, Bonjoch A, Puig J *et al.* Randomised study to assess the efficacy and safety of once-daily etravirine-based regimen as a switching strategy in HIV-infected patients receiving a protease inhibitor-containing regimen. Etraswitch study. *PLoS One* 2014; **9**: e84676.

Commented [CNS173]: Porter DP, Toma J, Tan Y et al. Clinical Outcomes of Virologically-Suppressed Patients with Pre-existing HIV-1 Drug Resistance Mutations Switching to Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate in the SPIRIT Study. HIV Clin Trials. 2016 Feb;17(1):29-37.. https://pubmed.ncbi.nlm.nih.gov/26899540/

Commented [LW174]: Palella FJ Jr, Fisher M, Tebas P, Gazzard B, Ruane P, Van Lunzen J, Shamblaw D, Flamm J, Ebrahimi R, Porter D, White K, Hindman J, Elbert E, De-Oertel S, Fralich T. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS. 2014 Jan 28;28(3):335-44.

Commented [LW175]: Johnson M, Kumar P, Molina JM, Rizzardini G, Cahn P, Bickel M, Mallolas J, Zhou Y, Morais C, Kumar S, Sklar P, Hanna GJ, Hwang C, Greaves W; DRIVE-SHIFT Study Group. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):463-472..

suppression (one experienced virological failure with emergent NNRTI and NRTI resistance and one had no data in the window at week 48) [REF]. DRIVE-BEYOND was designed to investigate the efficacy of doravirine/lamivudine/tenofovir-DF in virally suppressed people with selected NNRTI resistance mutations (K103N, Y181C or G190A), none of which are predicted to impact doravirine susceptibility [REF]. Unfortunately, only 10 people were recruited after more than a year and the trial was terminated early; all eight and seven participants who reached week 48 and week 96, respectively, maintained suppression but the sample size is far too small to draw meaningful conclusions. Therefore, we suggest not switching to NNRTI-based ART in the context of any NNRTI resistance.

5.10.3 NNRTI switch

Small studies investigating switching from efavirenz to alternative NNRTIs have demonstrated maintained virological efficacy with improvements in neuropsychiatric symptoms and lipid parameters [REFS].

STRATEGY-NNRTI investigated a randomised switch to tenofovir-DF/emtricitabine/elvitegravir/cobicistat versus continued NNRTI/two-NRTI-based ART, with most participants on efavirenz at baseline [REF]. The switch strategy was non-inferior from a virological efficacy perspective and, among people switching off efavirenz, was associated with improvements in CNS symptoms.

The TANGO and SALSA trials (both investigating switching from a suppressive three-drug regimen to dolutegravir/lamivudine) recruited some participants on an NNRTI at baseline: 13–14% in TANGO (12% were on rilpivirine) and 50% in SALSA (31% were on efavirenz) Efficacy was maintained but it is not possible to draw specific conclusions because of the absence of specific subanalyses or switch trials restricted to people on an NNRTI.

5.10.4 Integrase switch

The majority of TANGO participants (around 75%) were on coformulated tenofovir-DF/ emtricitabine/elvitegravir/cobicistat at baseline; switch to dolutegravir/lamivudine was associated with maintained virological efficacy and improvements in lipids and insulin sensitivity at week 48. Insulin sensitivity benefits were not maintained at later timepoints.
Approximately 40% of SALSA participants were on an INSTI at baseline: 17% dolutegravir, 10% elvitegravir/cobicistat, 10% bictegravir and 2% raltegravir. Again, virological efficacy was maintained but it is difficult to draw additional conclusions in the absence of specific subgroup analyses.

In GS-4030, people on a suppressive regimen of dolutegravir with tenofovir-AF/emtricitabine or tenofovir-DF/emtricitabine were randomly allocated to tenofovir-AF/emtricitabine/bictegravir or tenofovir-

Commented [LW176]: Palella FJ Jr, Fisher M, Tebas P, Gazzard B, Ruane P, Van Lunzen J, Shamblaw D, Flamm J, Ebrahimi R, Porter D, White K, Hindman J, Elbert E, De-Oertel S, Fralich T. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS. 2014 Jan 28;28(3):335-44.

Commented [LW177]: Wong A, Goldstein D, Mallolas J, DeJesus E, Johnson M, Molina JM, Pozniak A, Rodgers A, Teal V, Hepler D, Kumar S, Sklar P, Hanna GJ, Hwang C, Badshah C, Teppler H. Efficacy and Safety of Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) in Treatment-Naive Adults With HIV-1 and Transmitted Nonnucleoside Reverse Transcriptase Inhibitor Resistance Mutations. J Acquir Immune Defic Syndr. 2019 Dec 1;82(4):e47-e49..

Commented [LW178]: Waters L, Fisher M, Winston A *et al*. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS* 2011; **25**: 65–71.
Vera JH, Bracchi M, Alagaratnam J, Lwanga J, Fox J, Winston A, Boffito M, Nelson M. Improved Central Nervous System Symptoms in People with HIV without Objective Neuropsychiatric Complaints Switching from Efavirenz to Rilpivirine Containing cART. Brain Sci. 2019 Aug 9;9(8):195.

Commented [LW179]: Pozniak A, Markowitz M, Mills A, Stellbrink HJ, Antela A, Domingo P, Girard PM, Henry K, Nguyen T, Piontkowsky D, Garner W, White K, Guyer B. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. Lancet Infect Dis. 2014 Jul;14(7):590-9..

AF/emtricitabine plus dolutegravir (i.e. some people remained on the same backbone, some switched from tenofovir-DF to tenofovir-AF, some continued dolutegravir and some switched to bictegravir) [REF]. Maintained viral suppression rates, despite limited historical and proviral DNA evidence of NRTI resistance in some participants, were high and the only notable difference was greater weight gain in those switching from tenofovir-DF to tenofovir-AF compared to those already on tenofovir-AF at baseline.

Commented [LW180]: Sax PE, Rockstroh JK, Luetkemeyer AF, Yazdanpanah Y, Ward D, Trottier B, Rieger A, Liu H, Acosta R, Collins SE, Brainard DM, Martin H; GS-US-380–4030 Investigators. Switching to Bictegravir, Emtricitabine, and Tenofovir Alafenamide in Virologically Suppressed Adults With Human Immunodeficiency Virus. Clin Infect Dis. 2021 Jul 15;73(2):e485-e493.

5.11 Two-drug oral regimens: switching in virological suppression

Note: at the time of writing, two-drug regimens are not routinely recommended in pregnancy; please refer to the BHIVA guidelines for the management of HIV in pregnancy and postpartum for up-to-date guidance [REF].

Commented [CNS181]: BHIVA guidelines for the management of HIV in pregnancy and postpartum

5.11.1 Preferred options

5.11.1.1 Dolutegravir with lamivudine

Recommendations

We recommend that ART can be switched to dolutegravir with lamivudine in people with virological suppression (Grade 1A) but this regimen is **not** suitable for those:

- with a history of previous virological failure on an INSTI regimen or anti-retroviral resistance to lamivudine or INSTIs (Grade 1A);
- with hepatitis B co-infection (Grade 1A);
- at risk of hepatitis B who are not immune (GPP).

Rationale

The TANGO study recruited participants who had a stable, suppressed viral load and were treated with first-line, three-drug ART combinations containing tenofovir-AF/emtricitabine as the NRTI backbone [REF]. In approximately two-thirds of participants, the third agent was elvitegravir/cobicistat and about three-quarters were on a boosted regimen.

Exclusions included any history of major NRTI or INSTI resistance, hepatitis B infection, opportunistic disease other than cutaneous Kaposi's sarcoma with a CD4 count >200 cells/mm^3 and severe hepatic impairment. Participants were randomly assigned to continue their standard regimen or to switch to

Commented [LW182]: van Wyk J, Ajana F, Bisshop F *et al*. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study. *Clin Infect Dis* 2020; **71**: 1920–1929.

dolutegravir/lamivudine. Non-inferiority of the two-drug regimen was demonstrated at week 48. There was only one virological failure (in the tenofovir-AF/emtricitabine-based regimen group), and no emergent resistance was detected. Pro-viral DNA sequencing from baseline samples was undertaken and M184V was detected in four patients in the dolutegravir/lamivudine group (all of whom maintained viral suppression), but the clinical significance of proviral DNA detection is unclear. A slightly higher proportion of participants taking the two-drug regimen discontinued treatment because of adverse events, but the total number of these discontinuations was small.

Small but significantly different changes in metabolic parameters, such as lipids, were seen from baseline to week 48, favouring the two-drug regimen although when analysed by baseline ART this was limited to people on a boosted regimen [REF].

The SIMPL'HIV study was a randomised trial comparing dolutegravir/emtricitabine and continued standard three-drug regimens [REF]. Participants were required to have an undetectable viral load for 6 months prior to study entry, but a single viral load of <200 copies/mL was permitted during this time. After recruitment had commenced, a protocol amendment allowed the recruitment of individuals with a history of transmitted M184V mutation. A total of 188 participants were randomly assigned to treatment and non-inferiority of the two-drug arm was demonstrated at week 48 with a viral load cut-off of <100 copies/mL. Only one participant, assigned to the continued three-drug arm, had a documented M184V mutation. Virological failure was rare, and no new resistance was detected. Of note, dolutegravir/emtricitabine is not available as a fixed-dose combination.

Switching from a boosted PI to dolutegravir in virally suppressed people was investigated in TANGO [REF] and SALSA [REF]. TANGO excluded people with a history of major NRTI or INSTI resistance and SALSA excluded those who had previously switched therapy for suspected or confirmed virological failure. Both trials recruited people on a variety of regimens, and only 8% of participants in either trial were on a PI at baseline (mainly boosted darunavir); most TANGO participants were on elvitegravir/cobicistat-based ART and most recruited to SALSA were on an NNRTI (predominantly efavirenz). Both TANGO and SALSA demonstrated non-inferior virological efficacy.

5.11.1.2 Dolutegravir with rilpivirine

Recommendations

We suggest that ART can be switched to dolutegravir with rilpivirine in people with virological suppression (Grade 2A) but this regimen is **not** suitable for those:

- with a history of previous virological failure or anti-retroviral resistance to any NNRTI or INSTI (Grade 1A);
- those with hepatitis B co-infection (Grade 1A);

Commented [LW183]: Rockstroh JK, DeJesus E, Henry K *et al.* A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr* 2013; **62**: 483–486.

Commented [LW184]: Sculier D, Wandeler G, Yerly S et al. Efficacy and safety of dolutegravir plus emtricitabine versus standard ART for the maintenance of HIV-1 suppression: 48-week results of the factorial, randomized, non-inferiority SIMPL'HIV trial. *PLoS Med* 2020; **17**: e1003421

Commented [LW185]: van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla Sogorb J, Routy JP, Wyen C, Ait-Khaled M, Nascimento MC, Pappa KA, Wang R, Wright J, Tenorio AR, Wynne B, Aboud M, Gartland MJ, Smith KY. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose 2-Drug Regimen vs Continuing a Tenofovir Alafenamide-Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Phase 3, Randomized, Noninferiority TANGO Study. Clin Infect Dis. 2020 Nov 5;71(8):1920-1929..

Commented [LW186]: Llibre JM, Brites C, Cheng CY, Osiyemi O, Galera C, Hocqueloux L, Maggiolo F, Degen O, Taylor S, Blair E, Man C, Wynne B, Oyee J, Underwood M, Curtis L, Bontempo G, van Wyk J. Efficacy and Safety of Switching to the 2-Drug Regimen Dolutegravir/Lamivudine Versus Continuing a 3- or 4-Drug Regimen for Maintaining Virologic Suppression in Adults Living With HIV-1: Week 48 Results From the Phase 3, Non-inferiority SALSA Randomized Trial. Clin Infect Dis. 2022 Mar 2:ciac130. doi: 10.1093/cid/ciac130. Epub ahead of print. PMID: 35235656.

- those at risk of hepatis B who are not immune (GPP).

Rationale

Switching conventional three-drug treatment to dolutegravir with rilpivirine has been evaluated in the identically designed SWORD 1 and 2 open-label, randomised clinical trials [REF]. Eligible individuals were required to be receiving first-line or second-line ART. They were also required to have an undetectable viral load for at least 6 months and no viral load measurement of ≥200 copies/mL in the preceding 6–12 months. Any standard three-drug combination was allowed as a comparator, however participants were excluded if they had any history of antiretroviral resistance or virological failure. Non-inferiority of the two-drug regimen compared with continued three-drug treatment was demonstrated at week 48.

Drug-related neuropsychiatric adverse events were more common in the dolutegravir/rilpivirine arm, as were headache and diarrhoea. These side effects were responsible for the somewhat larger number of participants who discontinued dolutegravir/rilpivirine (total adverse events leading to discontinuation: *n*=17 [3%] for dolutegravir/rilpivirine; *n*=3 [1%] for continued three-drug regimen). There were few virological failures in each arm and the development of only one minor NNRTI mutation in the dolutegravir/rilpivirine arm. Although longer-term follow-up is available in the SWORD studies, randomised comparison was only undertaken until week 48 and therefore longitudinal data for this regimen are limited.

Commented [LW187]: Llibre JM, Hung CC, Brinson C et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2018; **391**: 839–849.

5.11.2 Acceptable in specific circumstances

5.11.2.1 Boosted PI with lamivudine

Recommendation

We suggest that three-drug boosted PI-based ART can be switched to two-drug boosted PI with lamivudine in people with virological suppression while taking into consideration that this regimen:

- Is **not** suitable for those with hepatitis B co-infection (Grade 1A).

No other oral two-drug regimens are recommended as switch strategies

Rationale

Four randomised studies have compared the use of a boosted PI plus lamivudine versus a conventional three-drug regimen in patients with a suppressed viral load [REFS].

Commented [LW188]: Pulido F, Ribera E, Lagarde M et al. Dual therapy with darunavir and ritonavir plus lamivudine vs triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of human immunodeficiency virus type 1 viral suppression: randomized, open-label, noninferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis* 2017; **65**: 2112–2118.
Di Giambenedetto S, Fabbiani M, Quiros Roldan E et al. Treatment simplification to atazanavir/ritonavir + lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48 week results from a randomized trial (ATLAS-M). *J Antimicrob Chemother* 2017; **72**: 1163–1171.
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.
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.

In the DUAL-GESIDA 8014-RIS-EST45 trial, darunavir/ritonavir plus lamivudine was found to be non-inferior to continued darunavir/ritonavir plus two NRTIs in individuals with no history of darunavir or lamivudine resistance [REF].

The ATLAS-M trial showed that atazanavir/ritonavir plus lamivudine was non-inferior (and superior in a *post hoc* analysis) to continued atazanavir/ritonavir plus two NRTIs [REF].

In the SALT study, switching to atazanavir/ritonavir plus lamivudine was non-inferior to continuing atazanavir/ritonavir plus two NRTIs in individuals suppressed on standard triple ART with no history of virological failure [REF].

The OLE study demonstrated that lopinavir/ritonavir plus lamivudine was non-inferior to continued lopinavir/ritonavir plus two NRTIs in individuals with no history of virological failure on, or resistance to, lamivudine or lopinavir [REF].

In general, non-PI-based ART is the option of choice but in individuals where a PI-based regimen is preferred, in the absence of hepatitis B co-infection, virological failure or lamivudine resistance, a boosted PI plus lamivudine can be used.

5.12 Two-drug injectable regimens: switching in virological suppression

Currently only one long-acting ART regimen is approved: long-acting cabotegravir/rilpivirine.

Recommendations

We recommend that long-acting cabotegravir/rilpivirine can be used in people who:

- Have a significant need for injectable ART (GPP) *and*
- Have been virally suppressed to <50 copies/mL for at least 6 months (Grade 1A) *and*
- Have no known or suspected NNRTI or INSTI resistance (Grade 1A) *and*
- Have no history of virological failure or unplanned treatment interruption on NNRTI- or INSTI-containing ART (Grade 1A) *and*
- Have no history of INSTI monotherapy (GPP) *and*
- Can commit to 2-monthly attendance for injections (GPP) *and*
- Accept the risk of virological failure despite complete adherence (approximately 1 in 70 at year 1 and 1 in 60 at year 2) (GPP) *and*

Commented [CNS189]: 6. Cahn P, Montaner J, Junod P *et al.* Pilot, randomized study assessing safety, tolerability and efficacy of simplified LPV/r maintenance therapy in HIV patients on the 1 PI-based regimen. *PLoS One* 2011; **6**: e23726.
Or should this be (as above):
Pulido F, Ribera E, Lagarde M et al. Dual therapy with darunavir and ritonavir plus lamivudine vs triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of human immunodeficiency virus type 1 viral suppression: randomized, open-label, noninferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis* 2017; **65**: 2112–2118.

Commented [LW190]: Di Giambenedetto S, Fabbiani M, Quiros Roldan E et al. Treatment simplification to atazanavir/ritonavir + lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48 week results from a randomized trial (ATLAS-M). *J Antimicrob Chemother* 2017; **72**: 1163–1171.

Commented [LW191]: 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.

Commented [CNS192]: 9. Katlama C, Valantin MA, Algarte-Genin M *et al.* Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS* 2010; **24**: 2365–2374.
Or should this be (as above):
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.

- Have a body mass index (BMI) of <30 kg/m^2 AND non-A1/6 subtype if baseline resistance is unavailable (Grade 1A) *and*
- Do not need a tenofovir-containing regimen for the treatment or prevention of hepatitis B (Grade 1A).

We recommend that long-acting cabotegravir/rilpivirine can be continued in people who:

- Have received long-acting cabotegravir/rilpivirine in a clinical trial (GPP);
- Are on long-acting cabotegravir/rilpivirine as part of a compassionate access or named patient programme (GPP).

We recommend the following viral load monitoring:

- HIV RNA quantification 2-monthly (Grade 1A);
- Prompt recall for repeat testing and resistance testing if viral rebound occurs (GPP).

Rationale

The initial registrational trials, ATLAS [REF] and FLAIR [REF], compared monthly long-acting cabotegravir/rilpivirine with continued oral therapy in virally suppressed people. Both trials demonstrated non-inferiority of injectable therapy for the primary endpoint of virological failure and key secondary endpoint of virological success. ATLAS-2M compared monthly long-acting cabotegravir/rilpivirine to a 2-monthly dosing schedule, demonstrating non-inferiority for the same primary and secondary endpoints at weeks 48 and 96 [REF]. There have been no direct comparisons of 2-monthly long-acting cabotegravir/rilpivirine versus oral therapy. HIV RNA quantification was performed at each visit in the trial so, until trial and/or real-world evidence emerges to support otherwise, we recommend viral load monitoring at all visits and prompt recall for repeat testing and resistance testing if viral rebound occurs.

The European Medicines Agency granted approval to both the monthly and 2-monthly long-acting cabotegravir/rilpivirine schedules, however the manufacturer is marketing only the 2-monthly option in the UK [REF].

The advent of long-acting treatment is an important milestone in the evolution of ART. It is, however, important to acknowledge that long-acting cabotegravir/rilpivirine has been investigated only in the context of viral suppression in a highly selected population and that data in more complex populations, including those with a history of virological failure or treatment interruption, are absent. Identifying people with adherence difficulties plus viral suppression may be challenging.

Commented [LW193]: Swindells S, Lutz T, Van Zyl L et al. Week 96 extension results of a Phase 3 study evaluating long-acting cabotegravir with rilpivirine for HIV-1 treatment. AIDS. 2022 Feb 1;36(2):185-194.

Commented [LW194]: Orkin C, Oka S, Philibert Pet al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. Lancet HIV. 2021 Apr;8(4):e185-e196.

Commented [LW195]: Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet HIV. 2021 Nov;8(11):e679-e689.

Commented [LW196]: Rekambys Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/12950/smpc#gref accessed 30 April 2022
Vocabria Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/12957/smpc#gref accessed 30 April 2022

5.12.1 Service capacity

The introduction of long-acting cabotegravir/rilpivirine will have major implications for services, in terms of staffing and the time required to support people to follow the strict dosing schedules. Although impact on services was included in the cost-effectiveness analyses undertaken by national approval bodies, there will be no extra funding for those costs, nor for the provision of pre-emptive supplies of oral bridging therapy should these be deemed necessary. It is worth noting that the estimated staff resource used to model costs in the National Institute for Health and Care Excellence (NICE) technology appraisal was 15 minutes of band 5 nurse time [REF].

Commented [LW197]: Cabotegravir with rilpivirine for treating HIV-1. NICE Technology appraisal guidance [TA757]. Published: 05 January 2022

We recommend a careful approach to initial use of long-acting cabotegravir/rilpivirine, recognising:

- The lack of data in a real-world setting;
- The consequences of virological failure (and the likelihood of dual-class resistance when it occurs);
- The variable capacity of services to deliver 2-monthly injections at a time when many are still relatively constrained secondary to the impact of COVID-19.

Services should therefore prioritise people most in need of injectable ART, who also meet the appropriate criteria, and ensure that staff are suitably trained to discuss the key data and support people living with HIV in making decisions about the suitability of long-acting cabotegravir/rilpivirine for them. Identifying people who struggle to manage daily pill taking but have managed to maintain viral suppression may be challenging. Patients should be confident that they can commit to 2-monthly injection appointments. We suggest that clinical services develop standard operating procedures to deliver injectable treatment, given the likely gradual accrual of people using this treatment and the need to schedule regular visits. There should be clear pathways to manage recall, missed appointments, cold chain requirements and the need for observation after injection administration.

While building capacity it is reasonable for services to focus on the following groups for access to long-acting cabotegravir/rilpivirine:

- Those most in need:
    - People who are known to or who express major psychological barriers to daily pill taking
    - People unable to take oral medication

  - People who describe a concerning adherence pattern but remain virally suppressed
  - People who describe a real risk of stopping ART if they continue oral therapy;
- Those already receiving long-acting cabotegravir/rilpivirine as part of a clinical trial or compassionate access programme;
- Clinics that have capacity and staffing to ensure that repeated, safe administration is possible (where individual services cannot meet the necessary requirement, they should work within their clinical networks to ensure equitable access) and have robust processes to manage and recall people who miss scheduled injection appointments.

Recommended criteria for long-acting cabotegravir/rilpivirine use

Based on the entry criteria for the ATLAS-2M trial, we recommend the following criteria for long-acting cabotegravir/rilpivirine use:

- Viral suppression to <50 copies/mL for at least 6 months *and*
- No known or suspected NNRTI or INSTI resistance *and*
- No history of virological failure on an NNRTI- or INSTI-containing regimen *and*
- No use of INSTI monotherapy *and*
- Ability to commit to 2-monthly attendance for intramuscular injections *and*
- Acceptance of a small risk of virological failure and resistance (approximately 1 in 70 at year 1 and 1 in 60 at year 2) *and*
- Where there are only one of the following: baseline rilpivirine polymorphisms, BMI greater than 30 kg/m^2 or subtype A6/A1, *and*
- No requirement for a tenofovir-containing regimen for the treatment or prevention of hepatitis B.

People should be counselled that:

- Known or suspected resistance to the either drug or detectable viraemia are exclusions;
- They will require an oral lead-in and then two deep gluteal intramuscular injections 1 month apart followed by deep gluteal intramuscular injections every 2 months in clinic;
- Implementation work shows they can expect to spend 30–60 minutes in clinic at each visit;
- Adherence is critical with a **maximum** +/– 7-day window for early/late administration; oral bridging can be used but should be considered an exception rather than routine;
- In clinical trials, about 1 in 70 people on 2-monthly long-acting cabotegravir/rilpivirine experienced viral rebound at year 1, and 1 in 60 at year 2, despite 100% adherence, and most of those also developed resistance to one or both drugs.

Long-acting cabotegravir/rilpivirine and pregnancy

There is limited information about injectable treatment in pregnancy so it is not a recommended option. Individuals wishing to conceive can remain on long-acting cabotegravir/rilpivirine. Those becoming pregnant on long-acting cabotegravir/rilpivirine should consult with their physician and come to a joint decision on whether to continue.

5.13 Protease inhibitor monotherapy

Recommendations

- We recommend against the use of PI monotherapy for routine ART (Grade 1A).

Auditable outcome

- Proportion of individuals on boosted PI monotherapy as an ART maintenance strategy and record of rationale.

Rationale

No new evidence has been considered for PI monotherapy; detailed guidance can be found in the 2015 BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy [REF].

PI monotherapy is associated with a small but significant increased risk of viral rebound compared to triple therapy (RR 0.95, 95% CI 0.9–0.99) although this was not associated with incident viral resistance, serious adverse events or compromised treatment options at 3-year follow-up [1-15]. Overall we do not consider that the potential benefits of PI monotherapy, in terms of drug resistance, long-term drug toxicity and cost, offset the risk of virological failure [16,17]. 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, or overdose, or acute illness). Where PI monotherapy is considered, darunavir/ritonavir (once or twice daily) or lopinavir/ritonavir (twice daily) should be used but with reintroduction of NRTIs if there is loss of virological control. Atazanavir/ritonavir monotherapy is not recommended because it has been associated with high rates of virological failure [18,19]. PI monotherapy is not recommended in individuals with active hepatitis B co-infection.

Commented [LW198]: 2015 BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy

Commented [CNS199]: Refs in list below:
1. Arribas JR, Delgado R, Arranz A *et al.* Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. *J Acquir Immune Defic Syndr* 2009; **51**: 147–152.
2. Arribas JR, Horban A, Gerstoft J *et al.* The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/mL. *AIDS* 2010; **24**: 223–230.
etc

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6 Supporting individuals on therapy

6.1 Adherence

6.1.1 Interventions to increase adherence to treatment

Recommendations

- We recommend that adherence and potential barriers to it are assessed and discussed with people living with HIV whenever ART is discussed, prescribed or dispensed (GPP).
- We recommend that adherence support should address both perceptual and practical barriers to adherence (GPP).
- Individuals experiencing difficulties with adherence should be offered additional support from staff within the multidisciplinary team with experience in adherence support and/or from organisations offering peer support (GPP).

Auditable outcomes

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

Rationale

High levels of adherence are important to achieve and maintain viral suppression; there is a marked reduction in viral suppression for even modern regimens among people reporting lower adherence [REFS]. Data from men enrolled in the Multicenter AIDS Cohort Study demonstrated that suboptimal adherence, in the context of maintained viral suppression, was associated with higher levels of inflammation although there may be additional confounders associated with suboptimal adherence [REF].

In the era of recommending that ART is started as soon as someone is ready, there may be less time to prepare individuals for lifelong treatment, so clear and repeated adherence advice is essential. Consultation with members of the multidisciplinary team who have experience in adherence support, such as pharmacists, psychologists and specialist nurses, and/or peer support 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 associated

Commented [LW200]: GEMINI, 1489 and 1490 studies as per main what to start

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with limitations in capacity or resources, which reduce the ability to adhere to the treatment as intended. Intentional non-adherence is the result of a decision informed by beliefs, emotions and preferences [REF].

Guidance on the monitoring of adherence to ART is available in the BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals [REF]. NICE has published detailed guidance on the assessment and support of adherence to medication in people with chronic diseases; key recommendations for adherence support are shown in Box 6.1 [REF]. As people may not raise adherence concerns, adherence should be checked routinely at every clinical visit.

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

Assessment
Recognise that non-adherence is common and that most individuals 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 individuals but rather to find out whether they need more information and support.
Make it easier for them to report non-adherence by: • 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 and stopping and starting medicines. If individuals are not taking their medicines, discuss with them whether this is because of beliefs and concerns or problems related to the medicines (intentional non-adherence) or because of practical problems (unintentional non-adherence). Find out what form of support they would prefer to increase their adherence to medicines.
Intervention
Individuals 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 each individual. Tailor any intervention to increase adherence to the specific difficulties with adherence the person is experiencing. Address any beliefs and concerns that result in reduced adherence. Interventions might include: • Suggesting that individuals record their medicine taking; • Encouraging them to monitor their condition;

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- Simplifying the dosing regimen;
- Using alternative packaging for the medicine;
- Using a multi-compartment medicines system.

Side effects can be a problem for some. If this is the case you should:

- Discuss how the individual would like to deal with side effects;
- Discuss the benefits, side effects and long-term effects with the individual 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 (e.g. timing of medicines).

6.1.2 Barriers to adherence

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

Commented [LW206]: Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013 Dec 2;8(12):e80633.

- 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.

A review of factors associated with ART uptake and adherence in the UK, Canada and Australia showed that beliefs about the necessity, efficacy, convenience and side effects of ART all affect adherence; three main categories of barriers were identified: intrapersonal, interpersonal and extrapersonal [REF] (Table 6.1).

Commented [LW207]: Bolsewicz K, Debattista J, Vallely A, Whittaker A, Fitzgerald L. Factors associated with antiretroviral treatment uptake and adherence: a review. Perspectives from Australia, Canada, and the United Kingdom. AIDS Care. 2015;27(12):1429-38. doi: 10.1080/09540121.2015.1114992..

Table 6.1 Categories of barriers to ART uptake and adherence

Intrapersonal	**Interpersonal**	**Extrapersonal**
Risk of disclosure	Not being connected to services	Lack of care coordination
Unwanted reminder of HIV status	Negative perceptions of provider's interpersonal skills, competency and confidentiality	Sociodemographic characteristics (employment, poverty, migration status, age at diagnosis, urban *vs* rural location, housing, ethnicity and sexuality)
Perceived lack of HIV-related illness and negative beliefs about health benefits of ART	Lack of provider recommendation to start/continue ART	Comorbidities and drug interactions
Low perceived readiness/self-efficacy around ART adherence		Drug use

Mental health symptoms and poor coping skills		Distance from clinic
Lack of knowledge about treatment and care		

A 2019 web-based survey from 25 countries showed that the commonest reasons for missing ART five times or more within the past month were feeling depressed or overwhelmed, trying to forget about HIV and work-related concerns [REF]. Correlates of suboptimal adherence included age under 50 years, education to high school equivalent or less, gastrointestinal side effects and privacy concerns. As people living with HIV age, the risk of multimorbidity increases; a systematic review revealed that, among people experiencing multimorbidity, non-adherence to medication for one condition did not necessarily extend to all conditions and, for example, people with HIV and tuberculosis (TB) reported higher adherence to medication for both conditions than those with HIV and chronic obstructive pulmonary disease [REF]. The same study confirmed earlier findings from studies focused on HIV [REFS] demonstrating that depression is associated with lower adherence, and that stronger belief in medication necessity correlated with better adherence.

6.1.2.1 Depression

Although depression is consistently associated with lower medication adherence, one study showed that lower rates of viral suppression were mitigated by treatment for depression [REF], consistent with an earlier study showing that adherence can be improved by treating depression [REF]. We recommend screening for depression prior to ART initiation and regularly thereafter in line with BHIVA monitoring guidelines [REF], as well as appropriate pathways for advice, referral and support as required. People living with HIV may benefit from being informed about the support options that are available to them locally, in line with the British Psychological Society/BHIVA/Medical Foundation for AIDS and Sexual Health standards for psychological support for adults living with HIV [REF].

6.1.2.2 Alcohol and drug use

Alcohol use, harmful or otherwise, is associated with lower ART adherence [REF]. The importance of accurate information provision is highlighted by a study demonstrating that intentional non-adherence may be explained by the inaccurate belief that it is hazardous to drink alcohol when taking medications [REF]. Similarly, recreational drug use has a negative impact on adherence and engagement in care [REF] and concerns about interactions with HIV medication may drive intentional non-adherence [REF]. Injecting drug use can also be associated with worse HIV treatment outcomes but opioid substitution therapy, and its

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integration within HIV services, improves adherence, viral suppression and retention in care [REF]. We recommend screening for alcohol and drug use prior to ART initiation and regularly thereafter in line with BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals [REF], as well as appropriate pathways for advice, referral and support as required.

6.1.2.3 Stigma

Stigma is a key factor associated with negative outcomes and the Positive Voices survey showed that one in four people with HIV experienced at least one stigma-related event within healthcare settings [REF]. Non-disclosure of HIV status is associated with lower ART adherence [REF] and peer support can foster improvements in self-esteem, confidence to share HIV status and ART adherence [REF]. People living with HIV should be referred to the BHIVA standards and advised how to raise concerns if they experience stigma during their care [REF].

6.1.2.4 Socioeconomic status

The ASTRA study revealed that after adjustment for demographic factors, increasing financial hardship and lack of employment, homeownership, university education and a supportive network were associated with higher risk of virological rebound in ART-treated individuals [REF]. Services refer individuals living with HIV to social support where necessary.

Community advocacy and peer support, including clinic-based peer support, are helpful in supporting an individual's understanding and confidence around treatments. Community organisations in the UK have been instrumental in providing a range of information resources for people living with HIV as well as 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.

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

- Elicit understanding of, and educate about, HIV and adherence in a way that is appropriate for the individual [REFS]. Similarly, review clinical outcomes in a way that is understandable.
- Provide a rationale for treatment that is tailored to the individual [REF].
- Clinicians should not contest beliefs of miraculous healing [REFS] but rather offer the compatible belief that medication and faith together can lead to healthy outcomes.
- Limit ART complexity and explore lifestyle, routine and work hours to select the most appropriate regimen [REF].

Commented [WLJ(ANWLN219]: Low AJ, Mburu G, Welton NJ, May MT, Davies CF, French C, Turner KM, Looker KJ, Christensen H, McLean S, Rhodes T, Platt L, Hickman M, Guise A, Vickerman P. Impact of Opioid Substitution Therapy on Antiretroviral Therapy Outcomes: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2016 Oct 15;63(8):1094-1104. doi: 10.1093/cid/ciw416. Epub 2016 Jun 25. PMID: 27343545; PMCID: PMC5036913.

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- Many people find it difficult to remember to take medication on time [REF]. Suggestions such as using an alarm [REF] 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 tablets with yoghurt to mask the taste.
- Suggest techniques to limit the risk of involuntary disclosure. HIV-related stigma can compromise adherence to ART [REFS], and not taking medication in front of others can be protective [REFS]. Injectable preparations may be an option where there is no resistance to the components of the parenteral regimen, and regular and timely attendance will not be compromised. Due to the long pharmacokinetic tail of injectable cabotegravir and rilpivirine, missed or late injections, without oral bridging cover, increase the risk of subtherapeutic drug exposure and development of resistance. Very limited data on the use of this regimen in individuals with poor engagement with care are available. Clinicians can offer alternative reasons to explain why someone might need to take medication at a particular time to decrease concern about disclosure (e.g. taking birth control, migraine or blood pressure medication).

6.1.3 Should the choice of first-line ART combination be affected by risk of non-adherence?

Recommendation

- Where there is clinical concern that doses may be missed intermittently, there is insufficient evidence to guide specific recommendations about ART choice. However, where there is a risk of frequent treatment interruptions, higher barrier regimens may be associated with less frequent selection for drug resistance (Grade 2C).

Rationale

Clinicians are poor at predicting adherence to ART [REFS]. The consequences of low adherence depend on drug pharmacokinetics, potency, fitness of resistant strains and genetic barrier to resistance.

There are no data from randomised controlled trials that directly address whether the choice of first-line ART combination should be affected by risk of non-adherence; people likely to be non-adherent may be excluded from such trials. Observational studies often select people living with HIV already established on ART [REFS] 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 experienced early virological failure or disease progression (or even death) or have defaulted from care. In addition, most

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studies predate the use of boosted-PI regimens and INSTIs with high genetic barriers to resistance in first-line therapy [REFS].

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

6.1.3.1 Effect of adherence on virological suppression

There are no data from randomised controlled trials that directly address the effect of adherence on virological suppression. Where the impact of adherence on viral suppression is reported, outcomes are usually reported by adherence greater than 95% versus 95% or less, though a cut-off of 90% is used in some studies.

In a randomised controlled trial comparing lopinavir/ritonavir with once-daily darunavir/ritonavir, virological failure was more likely in the lopinavir/ritonavir than the darunavir/ritonavir arm; there were no differences between the two arms when analysing individuals reporting >95% adherence [REF]. An association between efficacy and adherence has been demonstrated in randomised controlled trials of high-genetic barrier INSTI-based regimens.

The GS-US-380-1489 and GS-US-380-1490 studies evaluated the efficacy of bictegravir/emtricitabine/tenofovir-AF, compared to dolutegravir/abacavir/lamivudine and dolutegravir with emtricitabine/tenofovir-AF, respectively, in ART-naïve HIV-positive adults. Subgroup analyses were conducted stratifying subjects by adherence of <95% and ≥95%, based on tablet count. The GS-US-380-1489 results demonstrated that at <95% adherence, 81% who received bictegravir/emtricitabine/tenofovir-AF and 86% who received dolutegravir/abacavir/lamivudine achieved viral load suppression. Of those reporting ≥95% adherence, 97% who received bictegravir/emtricitabine/tenofovir-AF and 96% who received dolutegravir/abacavir/lamivudine achieved viral load suppression [REF]. The GS-US-380-1490 results demonstrated that of those reporting <95% adherence, 84% who received bictegravir/emtricitabine/tenofovir-AF and 90% who received dolutegravir with emtricitabine/tenofovir-AF were virologically supressed at week 48; of those reporting ≥95% adherence, 94% in both groups achieved suppression [REF]. Although differences were not statistically significant between study arms for either study, the numerical differences between the adherence strata for individual regimens indicate that adherence influences outcomes for these high-genetic barrier INSTI-based regimens.

A pooled *post hoc* analysis of the Gemini 1 and 2 studies evaluated the impact of treatment adherence on achieving viral load suppression at week 48 with dolutegravir and lamivudine dual therapy compared to dolutegravir with a tenofovir-DF/emtricitabine backbone [REF]. Analyses were conducted stratifying subjects

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by adherence of <90% and ≥90%, based on tablet count. The proportion of participants achieving viral suppression at week 48 was lower, and to a similar degree, among those with <90% adherence compared to those with ≥90% adherence for both treatment regimens [REF].

Much of the evidence on which adherence advice is based, including that at least 95% adherence is required to maintain viral suppression, was generated in the era of first-generation NNRTIs and unboosted PIs. More recent data suggest that many people will maintain viral suppression at lower levels of adherence. The association between adherence (based on percentage of days covered by ART over the previous 365 days) and viral suppression was examined in a cohort of 765 people [REF]. The odds ratio for viral suppression was the same for 80–90% adherence as for >90%; the overall estimated adherence level necessary to achieve viral suppression in 90% of viral load tests was 82% and varied by regimen type. INSTI-, NNRTI-and PI-based regimens achieved 90% viral suppression with adherence levels of 75%, 78% and 89% respectively.

6.1.3.2 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 [REFS]. The BREATHER trial investigated a '5 days on, 2 days off' strategy versus continued ART in participants aged 8 to 24 years with viral suppression on efavirenz plus two NRTIs [REF]. Non-inferiority was shown for short cycle therapy versus continuous therapy at 48 weeks, with similar resistance and a better safety profile. However, cycles of 7-day or 28-day treatment interruption resulted in failure of efavirenz and selection of resistance [REFS].

In the QUATUOR trial, 647 people on suppressive ART were randomly assigned to intermittent (4 days on, 3 days off) or continuous ART [REF]. At week 48, 96% in the intermittent treatment group and 97% in the continuous treatment group maintained viral suppression with virological failure rates of 2% and 1% respectively. Reported treatment satisfaction was significantly higher, and drug costs significantly lower, in the intermittent ART arm but resistance was more frequent: three of six participants who had virological failure developed emergent resistance compared to one of four in the continuous treatment. For boosted PI treatment, average adherence, rather than duration of treatment interruption, was associated with virological response in one study [REF].

Although these data may be helpful to reassure people who miss doses occasionally, this is not a strategy to be recommended routinely. However, in specific circumstances, structured intermittent therapy might be

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Commented [WLJ(ANWLN242]: Byrd, Kathy K. MD, MPHa; Hou, John G. PhDb; Hazen, Ron MPHb; Kirkham, Heather PhD, MPHb; Suzuki, Sumihiro PhDc; Clay, Patrick G. PharmDd; Bush, Tim MSa; Camp, Nasima M. MPHe; Weidle, Paul J. PharmD, MPHa; Delpino, Ambrose PharmDf; for the Patient-Centered HIV Care Model Team Antiretroviral Adherence Level Necessary for HIV Viral Suppression Using Real-World Data, JAIDS Journal of Acquired Immune Deficiency Syndromes: November 1, 2019 - Volume 82 - Issue 3 - p 245-251
doi: 10.1097/QAI.0000000000002142

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Dybul M, Nies-Kraske E, Daucher M *et al.* Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infectio ...

Commented [WLJ(ANWLN246]: Landman R, de Truchis P, Assoumou L, Lambert S, Bellet J, Amat K, Lefebvre B, Allavena C, Katlama C, Yazdanpanah Y, Molina JM, Petrov-Sanchez V, Gibowski S, Alvarez JC, Leibowitch J, Capeau J, Fellahi S, Duracinsky M, Morand-Joubert L, Costagliola D, Alvarez JC, Girard PM; ANRS 170 QUATUOR study group. A 4-days-on and 3-days- ...

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deemed an appropriate option, for example where stopping treatment at weekends reduces risk of longer treatment interruptions.

6.1.4 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 [REF]. A review of adherence interventions for ART included 19 studies (6312 adult individuals). Average adherence was modestly higher with once-daily 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 rates of 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 [REF]. Of note, this was based on non-randomised comparisons so there is a potential for confounding. NICE [REF] 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 virological suppression has been observed.

6.1.5 Fixed-dose combinations and single-tablet regimens

There are several fixed-dose combinations of ARVs, including single-tablet regimens. No meta-analyses on whether fixed-dose combinations or single-tablet regimens improve adherence, compared to the same components with a greater pill burden, 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 that use of fixed-dose combinations was associated with a significant reduction in the risk of non-adherence; however, in the single randomised controlled trial of treatment for HIV included in the analysis, no significant difference in treatment failure between groups receiving a fixed-dose combination versus non-fixed-dose combination was observed [REF]. A meta-analysis of cohort studies found that use of fixed-dose combinations for anti-hypertensive treatment was associated with increased adherence but with no improvement in blood pressure control [REF]. A randomised trial conducted in New Zealand showed that fixed-dose combinations resulted in significantly better adherence to primary prevention for CVD [REF].

A retrospective study of a pharmacy database found no benefit in persistence on first-line ART for any fixed-dose combination compared to separate agents [REF]. In the ECHO and THRIVE studies, a lower virological response rate in individuals with baseline viral load of 100,000–500,000 copies/mL was observed for rilpivirine- versus efavirenz-based regimens when given as separate agents [REF]; this finding was not

Commented [WLJ(ANWLN248]: Nieuwlaat R, Wilczynski N, Navarro T *et al.* Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014; **11**: CD000011.

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Commented [WLJ(ANWLN255]: Cohen CJ, Molina JM, Cassetti I *et al.* Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS* 2013; **27**: 939–950.

replicated when rilpivirine- and efavirenz-based regimens were formulated as fixed-dose combinations in the preliminary 48-week results from the STaR study [REF]. Although the use of fixed-dose combinations 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 potential advantage of single-tablet regimens 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 a difference in virological outcomes [REF]. Differential adherence was also reported in an Italian observational study; however, the difference was small and may have been confounded by other factors [REF].

An observational study of outcomes following a switch from a fixed-dose combination of efavirenz/emtricitabine/tenofovir-DF to multi-tablet regimens including swapping emtricitabine for lamivudine demonstrated maintained efficacy, and was safe and lower in cost [REF]. A retrospective analysis of switching from fixed-dose combinations to separate components in the Balearic Islands found lower pharmaceutical cost but higher overall healthcare cost in the first year following the switch [REF].

A systematic review and meta-analysis of single-tablet versus multi-tablet regimens demonstrated that single-tablet regimens are associated with significantly higher ART adherence levels at 95% and 90% thresholds. Findings from the systematic review showed that improved adherence results in an increased likelihood of achieving viral suppression in observational settings [REF]. A French cohort analysis showed that first-line therapy with single-tablet regimens was associated with a longer time to treatment discontinuation than with multi-tablet regimens but when ART modification for simplification was not considered as a failure, single-tablet and multi-tablet regimens were similar [REF].

Disadvantages of single-tablet regimens include cost, limited choice of regimens and the inability to adjust the dose for weight, renal impairment or drug–drug interactions. Although the licences for both lamivudine and emtricitabine as single components and within fixed-dose combination and single-tablet regimen preparations call for renal dose adjustment, there is evidence to support the use of higher doses in renal impairment. With dose adjustment based on eGFR, there is a risk of under dosing, particularly in the presence of drugs that inhibit tubular secretion of creatinine, and subsequent underestimation of eGFR. Studies have demonstrated good tolerability and minimal toxicity resulting from accumulation of either drug [REFS]. These data are limited and any decision to deviate from licensed dosing should be made based on the individual's clinical circumstances including stage of renal failure, modality of renal replacement therapy and ability to manage complex administration including liquid formulations.

Commented [WLJ(ANWLN256]: Cohen C, Wohl D, Arribas J *et al.* STaR Study: single-tablet regimen emtricitabine/rilpivirine/tenofovir DF is non-inferior to efavirenz/emtricitabine/tenofovir DF in ART-naïve adults week 48 results. *11th International Congress on Drug Therapy in HIV Infection*. November 2012. Glasgow, Scotland. Abstract 425.

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In summary, fixed-dose combinations and single-tablet regimens support adherence to treatment, and this may reduce the risk of virological failure. However, the size of this effect is uncertain, and needs to be balanced against the potentially far lower cost of generic ARV agents. When considering the need for a fixed-dose combination or single-tablet regimen, ARV pill burden should be considered in the context of concomitant medication taken for other conditions.

6.2 Pharmacology

For managing HIV, as for any long-term condition (and arguably more so due to the consequences of treatment failure), healthcare professionals need to have a clear understanding of the basic principles of pharmacology to ensure effective and appropriate prescribing. We focus on four key areas: drug interactions, stopping therapy, switching therapy and TDM.

6.2.1 Drug interactions

Recommendations

- Drug histories should be taken at each clinic visit, and a full medication history (including herbal medicines, recreational drugs and other non-prescribed medications) should be taken at least annually (GPP).
- All potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications should be checked before administration (GPP).
- Wherever feasible, people living with HIV should be counselled about the risks of drug interactions, and advised to use resources such as the University of Liverpool HIV Drug Interactions app (iOS or Android) (GPP).

Auditable outcomes

- Record in medical notes of full medication history at least annually.
- Record in medical notes of potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications.
- Record of communication regarding key drug–drug interactions with GPs and other key healthcare professionals.

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 ARVs 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: steroids (including topical, inhaled and local injections), quetiapine, acid-reducing agents, methadone, oral contraceptives, anti-epileptics, antidepressants, lipid-lowering agents, certain antimicrobials (e.g. clarithromycin, minocycline and fluconazole), some anti-arrhythmics, anti-TB therapies, anti-cancer drugs, immunosuppressants, phosphodiesterase inhibitors and anti-hepatitis C virus 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, and inhaled fluticasone and ritonavir/cobicistat) the nature of the interaction is such that co-administration must be avoided and alternatives sought.

It is important that education about the risks of drug interactions, including over-the-counter or recreational drugs, should be provided and people living with HIV should be encouraged to discuss the risks with pharmacists or their healthcare professionals before commencing any new drugs, including those prescribed in primary care.

High-risk scenarios for harmful drug–drug interactions are those involving non-oral co-medications (especially steroids that are inhaled or injected locally), or those involving multiple teams (such as is the case with multiple morbidities, or in acutely unwell patients). In these cases, teams may lack full knowledge of medicines and their drug–drug interaction liabilities, and harms may be wrongly attributed to underlying disease. Large surveys have shown that about a third to a quarter of people living with HIV receiving ART are at risk of a clinically significant drug interaction [REFS]. 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 [REF] and within hospital settings particularly when multiple teams are involved, or when medical records are fragmented (e.g. with separate HIV case notes) [REF].

A UK survey found that even when medication recording is complete, physicians were only able to identify correctly one-third of clinically significant interactions involving HIV drugs [REF].

In patients who are acutely unwell and medically unstable there are several potential risks and early engagement with specialist pharmacists and use of appropriate resources is advised; risks include:

Commented [LW264]: Okoli C, Schwenk A, Radford M *et al.* Polypharmacy and potential drug-drug interactions for people with HIV in the UK from the Climate-HIV database. *HIV Med* 2020; **21**: 471–480.
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- Lack of recognition of the interaction potential of rifampicin given outside of TB treatment (e.g. for severe and complex *Staphylococcus* infections);
- The routine prescribing of vitamin supplements in patients with malignancies;
- The routine prescribing of sodium bicarbonate or calcium supplements in patients with renal disease;
- Continuing medications that have potential toxicities and do not contribute significantly to acute management (e.g. statins and acid-reducing agents); temporarily discontinuing such medications should be considered. Hypoalbuminaemia is common in acutely unwell patients and competition for protein binding can result in higher concentrations of free drug and increased risk of toxicity of highly protein-bound drugs. Consideration should be given to this when rationalising treatment;
- Some clinical scenarios may necessitate administration of medication and feeds via enteral tubes, which may further potentiate malabsorption or drug–drug interactions.

6.2.1.1 Specialist advice

In addition to HIV specialist and local pharmacists, the University of Liverpool's comprehensive drug interaction website [REF] is an excellent and highly recommended resource for information relating to potential drug interactions; the website also includes specific resources such as dosing in renal impairment, managing people who cannot take oral medication and considerations for bariatric surgery. Additional information resources include the electronic medicines compendium [REF], summaries of product characteristics and medical information departments of pharmaceutical companies.

Commented [LW268]: www.hiv-druginteractions.org

Commented [CNS269]: www.medicines.org.uk/emc

Communication with GPs and other medical specialists involved in care is fundamental for minimising the risk of adverse drug interactions. All clinic letters should carry as a standard header or footer advice to check for interactions, with links to appropriate resources to address the potential for drug interactions, and should flag particularly important drug–drug interactions if possible. Where drug–drug interactions are identified, there should be appropriate reporting and feedback to the relevant prescribers/teams. Peer support may help individuals understand the need for open and clear discussion with their HIV team about drug–drug interactions, particularly as people may not feel comfortable telling healthcare professionals about recreational drug use or may not appreciate the potential importance of non-prescribed medication and supplements.

6.2.2 Stopping therapy: pharmacological considerations

Recommendations

- For individuals discontinuing ART containing efavirenz or nevirapine in combination with an NRTI backbone, we recommend that all drugs are replaced with a PI (darunavir/ritonavir once daily) for 4 weeks (Grade 1C).
- We strongly recommend against abrupt cessation of long-acting cabotegravir/rilpivirine due to a high risk of resistance emergence (Grade 1D).
- For individuals stopping any other regimen, we recommend that all drugs are stopped simultaneously, and no replacement is required (Grade 1C).

Rationale

In general, treatment interruptions are not recommended for most individuals. Whatever the reason for stopping ART (e.g. intercurrent illness 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.

NRTI and NNRTI resistance mutations have been detected following discontinuation of previously suppressive NRTI + NNRTI regimens [REF] 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 [REF], and choice is influenced by clinical considerations, individual preferences 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 have been no randomised comparisons of these three strategies. However, in one study, fewer emergent resistance mutations were seen in those switching to a PI compared with those undergoing a simultaneous or staggered stop [REF]. 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 be inadequate to prevent emergence of NNRTI mutations [REF]. The optimal duration of replacement with a PI is not known, but 4 weeks is probably advisable.

The long-acting injectable preparations of cabotegravir and rilpivirine have long pharmacokinetic tails with marked interindividual variability, and subtherapeutic concentrations of drug have been detected for more

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than a year after the last injection in some individuals [REFS]. This highlights the importance of initiating these preparations in individuals who are likely to remain engaged with care and unlikely to experience treatment interruptions. We strongly recommend against abrupt ART cessation and suggest that a fully active oral regimen is initiated within one dosing interval if stopping an injectable regimen to prevent development of viral rebound and resistance.

Commented [LW274]: Spreen W, Min S, Ford SL *et al.* Pharmacokinetics, safety, and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. *HIV Clin Trials* 2013; **14**: 192–203.
Verloes R, Deleu S, Niemeijer N *et al.* Safety, tolerability and pharmacokinetics of rilpivirine following administration of a long-acting formulation in healthy volunteers. *HIV Med* 2015; **16**: 477–484.

6.2.3 Switching therapy: pharmacological considerations

Recommendations

- Despite the potential for altered concentrations of the replacement drug when switching from efavirenz or nevirapine, in the context of viral suppression we recommend a direct switch without dose adjustment (Grade 1D).
- If switching from etravirine to dolutegravir, we recommend increasing the dolutegravir dose to 50 mg twice daily for the first 14 days (GPP).
- We recommend against omitting the oral lead-in when switching from efavirenz, nevirapine or etravirine to long-acting cabotegravir/rilpivirine (GPP).
- We recommend monthly dosing of long-acting cabotegravir/rilpivirine for the first 3 months if switching directly from efavirenz or etravirine (GPP).
- We recommend careful consideration of the impact on concomitant non-ARV medications if switching from a boosted to unboosted regimen (GPP).

Rationale

Switching a component of an ART regimen is frequently considered in people living with HIV 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. Whether viral load is maximally suppressed should also be considered when planning how to switch away from efavirenz to an alternative agent.

Strategies for switching to an alternative agent where there may be pharmacological consequences are summarised below.

6.2.3.1 Switching from efavirenz (or nevirapine) to alternative oral agents

Efavirenz is classified as a moderate inducer and nevirapine as a weak-to-moderate inducer of cytochrome P45 (CYP)3A and glucuronidation.

It has been shown that switching from efavirenz to etravirine or rilpivirine, or nevirapine to rilpivirine [REF], in people living with HIV with an undetectable viral load does not compromise virological responses, as undetectable viral loads were maintained despite the transitional lower drug plasma concentrations post-switch [REF]. It has also been shown that increasing the dosage of maraviroc to 600 mg twice daily for 7 days following the switch from efavirenz overcomes the persistence of efavirenz post-switch induction and contributes to maintaining an undetectable viral load [REF]. A transient decrease in doravirine [REF] and elvitegravir [REFS] concentrations was observed following switching from efavirenz but in the context of viral suppression the significance of this remains unknown. There is some impact of a direct switch from efavirenz on raltegravir [REF] and dolutegravir [REF] pharmacokinetics, and some impact of a direct switch from nevirapine on dolutegravir pharmacokinetics [REF] but these are not considered clinically important and no dose adjustment is recommended.

Hence, we have taken the view that (where specific data on switching are lacking) unless there is evidence of a major risk of toxicity or failure when switching from a moderate inhibitor or inducer, a straightforward substitution should be presumed to be reasonable. However, if switching away from efavirenz is undertaken when viral load is likely to still be detectable, substitution with a boosted PI in preference to a within-class switch is advised.

6.2.3.2 Switching from etravirine to alternative oral agents

Modern regimens are associated with higher inhibitory quotients, which provide greater resilience against short-term falls in plasma drug concentrations.

Etravirine is a potent inducer of CYP3A and glucuronidation, reducing dolutegravir exposure by 71% (in the absence of any protective effect of a concomitant boosted PI) [REF] but raltegravir exposure by only 10% [REF]. Therefore, we recommend a straightforward substitution of etravirine with raltegravir, and a doubling of dolutegravir to 50 mg twice daily for the first 14 days after stopping etravirine, especially in people with a detectable viral load.

Data on switching from etravirine to other core agents, including elvitegravir/cobicistat, doravirine or bictegravir, are not available. It is expected that such switches would result in significantly lowered concentrations for the first 14 days. Because dose increment is not an option for these regimens, we recommend switching directly in people with an undetectable viral load, and then monitoring viral load.

Commented [WLJ(ANWLN275]: Allavena C, Dailly E, Reliquet V *et al.* Switching from tenofovir/emtricitabine and nevirapine to a tenofovir/emtricitabine/rilpivirine single-tablet regimen in virologically suppressed, HIV-1-infected subjects. *J Antimicrob Chemother* 2014; **69**: 2804–2808.

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Commented [LW277]: Waters L, Jackson A, Else L *et al.* Switching safely: pharmacokinetics, efficacy and safety of switching efavirenz to maraviroc twice daily in patients on suppressive antiretroviral therapy. *Antivir Ther* 2015; **20**: 157–163.

Commented [LW278]: Yee KL, Sanchez RI, Auger P, Liu R, Fan L, Triantafyllou I, Lai MT, Di Spirito M, Iwamoto M, Khalilieh SG. Evaluation of Doravirine Pharmacokinetics When Switching from Efavirenz to Doravirine in Healthy Subjects. Antimicrob Agents Chemother. 2017 Jan 24;61(2):e01757-16.

Commented [LW279]: Cohen C, Elion R, Ruane P *et al.* Switch from efavirenz/emtricitabine/tenofovir DF to elvitegravir/cobicistat/emtricitabine/tenofovir DF: efficacy and pharmacokinetics. *53rd ICAAC*. September 2013. Denver, CO, USA. Abstract H-658.
Pozniak A, Markowitz M, Mills A *et al.* Switching to coformulated elvitegravir, cobicistat, emtricitabine, and ...

Commented [LW280]: Iwamoto M, Wenning LA, Petry AS *et al.* Minimal effects of ritonavir and efavirenz on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother* 2008; **52**: 4338–4343.

Commented [LW281]: Generaux G, Song I, Bowers G, Piscitelli S. A mechanistic SimCYP simulation evaluating dolutegravir and efavirenz pharmacokinetics following a switch from once-daily efavirenz to once-daily dolutegravir. *15th International Workshop on Clinical Pharmacology of H* ...

Commented [WLJ(ANWLN282]: Dailly E, Allavena C, Gregoire M *et al.* Influence of nevirapine administration on the pharmacokinetics of dolutegravir in patients infected with HIV-1. *J Antimicrob Chemother* 2015.

Commented [LW283]: Song et al. 2011 https://journals.asm.org/doi/10.1128/AAC.00073-11

Commented [LW284]: Ford et al 2013. https://journals.asm.org/doi/10.1128/aac.01685-12?permanently=true

6.2.3.3 Switching from efavirenz, etravirine or nevirapine to long-acting cabotegravir/rilpivirine

Efavirenz and etravirine are examples of moderate enzyme inducers and, as noted above, nevirapine is a weak-to-moderate inducer of CYP3A. Residual induction (persisting for up to 2 weeks after their discontinuation) may decrease concentrations of rilpivirine (more so than cabotegravir) which also has a low-genetic barrier to resistance. Additionally, following intramuscular administration (in the absence of oral cabotegravir/rilpivirine lead-in) it takes several months for steady-state levels of these agents to be reached. The majority of participants in ATLAS and ATLAS-2M [REFS] switched from NNRTI-containing regimens (most commonly efavirenz: 32% and 39% in ATLAS and ATLAS-2M respectively) where the dose of oral rilpivirine was not increased. Additionally, pooled pharmacokinetic analyses from SWORD-1 and SWORD-2 [REF] suggested that rilpivirine trough concentrations were comparable to historical controls at weeks 4, 24 and 48 following switch. Collectively these considerations have informed our recommendations for managing a switch to long-acting cabotegravir/rilpivirine from regimens containing efavirenz, etravirine and nevirapine.

- We recommend against omitting the oral lead-in (in the absence of pharmacokinetic data) when switching from efavirenz or etravirine (GPP). An oral lead-in period of 4 weeks is recommended for patients switching from efavirenz/etravirine (GPP), comprising:
  - Oral cabotegravir and higher-dose oral rilpivirine (50 mg) for 2 weeks followed by 2 weeks of standard dosing *or*
  - Standard-dose oral cabotegravir and rilpivirine with additional two-NRTI cover from tenofovir-DF (or tenofovir-AF) plus emtricitabine or lamivudine.

  Although no significant drug–drug interaction is anticipated [REF], we also recommend a 4-week oral cabotegravir/rilpivirine lead-in period when switching from nevirapine (GPP).
- We recommend 4-weekly intramuscular cabotegravir/rilpivirine in the first instance when switching from efavirenz- or etravirine-based therapy. Consideration can be given to 2-monthly injections after the first 3 months (GPP).

6.2.3.4 Switching from a boosted PI to any regimen

The virological, tolerability and toxicity-associated benefits of switching away from a boosted PI have been demonstrated in a number of studies, and switching away from a PI is now more common due to evolving evidence to support the use of high-genetic barrier INSTI-based regimens in treatment-experienced individuals. Removal of a pharmacokinetic enhancer from a regimen often results in alteration of levels of concomitant non-ARV drugs and subsequent toxicity or reduction in efficacy, and close monitoring and dose adjustment may be required particularly in the case of agents that have a narrow therapeutic index. Taking a

Commented [LW285]: ATLAS & ATLAS-2M

Commented [CNS286]: Adkison et al 18th International Workshop on Clinical Pharmacology of Antiviral Therapy June 14-17, 2017 https://www.natap.org/2017/Pharm/Pharm_22.htm

Commented [WLJ(ANWLN287]: Allavena C, Dailly E, Reliquet V *et al.* Switching from tenofovir/emtricitabine and nevirapine to a tenofovir/emtricitabine/rilpivirine single-tablet regimen in virologically suppressed, HIV-1-infected subjects. *J Antimicrob Chemother* 2014; **69**: 2804–2808.

thorough drug history in advance of the switch is essential, and cross-disciplinary communication is key in managing such modifications.

6.2.4 TDM

Recommendations

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

Rationale

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 tolerability of modern ARV regimens, which are associated with higher therapeutic indices and inhibitory quotients, the role of TDM in clinical management has also evolved in the context of selected groups and clinical situations. A Cochrane review of randomised controlled trials [REF] suggested little value of TDM when used unselectively. However, TDM may inform the management of vulnerable populations or complex clinical situations.

6.2.4.1 Monitoring adherence

While detection of drug at therapeutic or even high plasma concentrations does not exclude low adherence, absence of measurable drug, or presence of very low drug levels, strongly suggests 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 reported adherence, virological rebound, particularly in the absence of any resistance mutations, and other features in the history that suggest risk of low treatment adherence.

6.2.4.2 Optimising treatment in specific populations

TDM may have a role in optimising therapy in specific populations (e.g. children, pregnant women [REF] and individuals with extremes of BMI) or in specific clinical situations (e.g. liver and renal impairment, treatment failure, foreseen and unanticipated drug interactions, malabsorption, suspected non-adherence and unlicensed once-daily dosing regimens). Higher concentrations of PIs have been observed in ageing populations, and evidence of ARV toxicity resulting from drug accumulation due to altered drug pharmacokinetics is a concern [REFS]. Although TDM may be beneficial in ageing populations, further

Commented [WLJ(ANWLN288]: Kredo T, Van der Walt JS, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. *Cochrane Database Syst Rev* 2009; Cd007268.

Commented [WLJ(ANWLN289]: Andany N, Loutfy MR. HIV protease inhibitors in pregnancy : pharmacology and clinical use. *Drugs* 2013; **73**: 229–247.

Commented [WLJ(ANWLN290]: Angus B, Brook G, Awosusi F *et al*. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals (2019 interim update). Available at: https://www.bhiva.org/file/DqZbRxfzlYtLg/Monitoring-Guidelines.pdf (accessed March 2022).
Winston A, Jose S, Gibbons S *et al*. Effects of age on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring. *J Antimicrob Chemother* 2013; **68**: 1354–1359.
Avihingsanon A, Kerr SJ, Punyawudho B *et al*. Short communication: aging not gender is associated with high atazanavir plasma concentrations in Asian HIV-infected patients. *AIDS Res Hum Retroviruses* 2013; **29**: 1541–1546.

evidence for its role in routine management is needed; in the absence of further data, management should be guided by virological control, signs and symptoms of toxicity and the need to optimise ART. In scenarios in which TDM is used to guide dosing, the aim is either to optimise dosing based on known efficacy or toxicity cut-offs or to achieve the range of plasma concentrations observed in pharmacokinetic studies at licensed treatment doses.

6.2.4.3 Managing drug interactions

Where the ARV drug has the potential to be adversely affected by another drug, and the combination is unavoidable, TDM may be used either to manage the interaction or to discount a significant interaction in a particular individual.

6.2.4.4 Other situations

Knowledge of plasma drug concentrations may be clinically useful when evaluating whether there is scope for treatment simplification, or for confirming or refuting impaired drug absorption as a reason for virological failure.

As for all other investigations, it is essential that TDM is undertaken correctly, especially with regard to timing (i.e. when steady state has been achieved). A consensus has been reached for defining targets [REF] 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.

Commented [WLJ(ANWLN291]: La Porte C, Back D, Blaschke T *et al.* Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. *Rev Antivir Ther* 2006; **3**: 4–14.

7 Managing virological failure

7.1 Introduction

Detailed guidance on HIV viral load, resistance and genotypic tropism testing can be found in the BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals [REF].

Commented [CNS292]: BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals 2016 (2019 interim update)

The following recommendations concern the management of people living with HIV experiencing virological failure on ART. Populations experiencing virological failure will include those with no or limited HIV drug resistance, those with more extensive resistance or historical virological failure on NRTIs, NNRTIs, PIs and/or INSTIs and those with limited treatment options. 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 due to 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.

In the UK, the cumulative virological failure rate after 4 years on first-line therapy was estimated to be 8%, 12% and 25%, respectively, for NNRTI-, INSTI- and PI-based regimens [REF]. 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 TDR and failure to adapt first-line treatment [REFS].

Commented [CNS293]: 3. Wittkop L, Gunthard HF, de Wolf F *et al.* Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infect Dis* 2011; **11**: 363–371.
4. Kuritzkes DR, Lalama CM, Ribaudo HJ *et al.* Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis* 2008; **197**: 867–870.

The general principles for the management of individuals experiencing virological failure are outlined in Boxes 7.1 and 7.2 (all 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.

Auditable outcomes

- Record in medical notes of resistance result at baseline (HIV diagnosis) or at ART initiation (if former not available) and at first viral load >200 copies/mL after prior virological suppression (or less if successful genotyping) 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 who now have an undetectable viral load.
- Record of individuals with multi-class virological failure with or without multi-class resistance being discussed within a multidisciplinary team and/or referred for 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 viral load below the lower limit of detection of the assay being used (may vary between centres).

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

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

Virological rebound: failure to maintain viral load below the limit of detection on two or more consecutive tests.

Low-level viraemia: a confirmed viral load between 50 and 200 copies/mL.

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

Recommendations

In individuals on ART:

- A single viral load of 50–200 copies/mL preceded and followed by an undetectable viral load is usually not a cause for clinical concern (GPP). It should necessitate clinical vigilance, adherence reinforcement, a search for possible interactions and repeat testing within 2–6 weeks depending on ARV regimen.
- We recommend that a single viral load of >200 copies/mL is investigated further, including a rapid re-test with/without genotypic resistance testing, as it may be indicative of virological failure (Grade 1C).

- We recommend that in the context of low-level viraemia or repeated viral blips, resistance testing should be attempted (Grade 1D).
- We recommend that in the context of low-level viraemia or repeated blips a high genetic barrier regimen should be used (GPP).

Rationale

7.2.1 Blips

Optimal HIV control is ordinarily reflected by complete virological suppression with an undetectable viral load. A virological blip is variably defined but for the purposes of these guidelines the definition that has been adopted is a detectable viral load between 50 and 200 copies/mL, which is preceded and followed by an undetectable result without any change of therapy. Blips occur frequently. One study reported a median value of 79 copies/mL and, when real and not due to laboratory variability, blips 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 shown an association between blips and future virological failure [6,11].

There is a correlation between level of first detectable viral load and subsequent virological rebound [8,12]. One retrospective study of more than 3000 individuals found virological failure (defined as consecutive HIV viral load >50 copies/mL measured at least 30 days apart, or any viral load >1000 copies/mL) in 26%; 14% of rebounds were preceded by transient HIV viral load of 50–999 copies/mL but, critically, only transient HIV viral load >500 copies/mL correlated with rebound in multivariable analyses [12]. This is consistent with findings from other studies (see Section 7.2.2 Low-level viraemia).

Viral load 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 [9,13,14]. Most individuals with short-lived increases in HIV viral load 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 viral load (see Section 7.2.2 Low-level viraemia) run a higher risk of virological failure. In keeping with the DHSS guidance [REF], in these guidelines we 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 a search for any tolerability/toxicity issues, drug–drug and drug–food interactions and evidence of archived resistance. A viral load of 50–200 copies/mL preceded and followed by an undetectable

Commented [CNS294]: 5. Havlir DV, Bassett R, Levitan D *et al.* Prevalence and predictive value of intermittent viremia with combination hiv therapy. *JAMA* 2001; **286**: 171–179.
6. Greub G, Cozzi-Lepri A, Ledergerber B *et al.* Intermittent and sustained low-level HIV viral rebound in patients receiving potent antiretroviral therapy. *AIDS* 2002; **16**: 1967–1969.
7. Nettles RE and Kieffer TL. Update on HIV-1 viral load blips. *Curr Opin HIV AIDS* 2006; **1**: 157–161.

Commented [CNS295]: DHSS guidance:
16. DHSS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. 2014. Available at: http://aidsinfo.nih.gov/guidelines (accessed September 2015).

viral load should not be a cause of clinical concern. In the context of repeated blips or persistent low-level viraemia, genotypic resistance testing is recommended [11,17].

7.2.2 Low-level viraemia

Low-level viraemia is observed in up to 8% of individuals [18] and, when compared to viral suppression to <50 copies/mL, is associated with an increased risk of virological failure and resistance [6,19,20]. The likelihood of resuppression after low-level viraemia is greater for lower magnitudes of viraemia [21]. Indeed it is uncertain whether viraemia <200 copies/mL always confers independent risks as viraemia at this level may reflect assay variation. Low-level viraemia is associated with resistance (37% in one study [20]) that may be associated with the magnitude of viraemia; in one analysis, maximum viral load was higher in those who developed resistance (368 *vs* 143 copies/mL; *P*=0.008). In cohort studies [19] and clinical trials [20], individuals on boosted PI-based ART were more likely to experience detectable viraemia than those on an NNRTI-based regimen. Many individuals with low-level viraemia have low or undetectable plasma drug levels in untimed samples underscoring the importance of assessing adherence [22]; however, we do not recommend routine TDM in this context (see Section 6.2.4 TDM) . Low-level viraemia 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 low-level viraemia (viraemia between 50 and 200 copies/mL) on treatment. Where resistance is detected, regimens should be modified appropriately. In the absence of clear data, it is the view of the writing group that persistent low-level viraemia or recurrent blips on a low-genetic barrier regimen (including NNRTI-based or first-generation INSTI-based therapy), even in the absence of detectable resistance, warrants prompt regimen change to a high genetic barrier regimen [23,24]. Of note, intensifying ART in the context of low-level viraemia or recurrent blips is not usually effective.

Further evaluation should follow as outlined in Box 7.1.

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

- Factors affecting adherence and drug exposure, including tolerability/toxicity issues, drug–drug /drug–food interactions, ARV potency, significant renal/liver disease and mental health/drug dependency problems should be evaluated.
- Resistance testing should be performed while on failing therapy or within 2–4 weeks of discontinuation.

- Past ART and resistance tests should be reviewed for archived mutations.
- Tropism testing should be performed if maraviroc is being considered.
- Intensification with a single additional active ARV is not recommended.
- Once virological failure is confirmed and preferably after a resistance test result is available, the regimen should be changed as soon as possible to avoid accumulation of resistance mutations.
- When switching regimens, factors such as drug–drug interactions and patient characteristics such as hepatitis B virus status should be considered. Where necessary, drugs that are active against hepatitis B should be continued.

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 and drug–food interactions, comorbidities and future therapy options. The goal of the new combination is to re-establish a viral load <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 are unclear. Several studies have evaluated the risk of virological rebound to >50 copies/mL in individuals with detectable viraemia <50 copies/mL; results are conflicting [25-27]. In one study, subjects were stratified based on the Abbott RealTime Assay into viral load 40–49 copies/mL, <40 copies/mL with RNA detected and <40 copies/mL with no RNA detected [26]. It was found that compared to individuals with viral load <40 copies/mL and no detected RNA, viraemia of 40–49 copies/mL increased the risk of rebound to >50 copies/mL by 4.67-fold while a 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 found increased risk of rebound to >50, >200 and >400 copies/mL but, importantly, not ≥1000 copies/mL [28]. The majority of the rebounds to >200 copies/mL were blips and resistance rarely emerged [28], making the significance of these events unclear.

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

7.2.3 Virological failure

In the UK, among drug-experienced individuals who experience virological failure, approximately 70% have no major resistance mutations on genotypic resistance testing [29]. Confirmation of virological failure at any stage should lead to the practice shown in Box 7.1.

Box 7.2. Best practice for the management of individuals with multi-class virological failure (all GPPs)

- In individuals with ongoing viraemia and with few 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 boosted PI (preferably ritonavir- or cobicistat-boosted darunavir) and one agent with a novel mechanism of action (these may include INSTIs, CCR5 antagonists, molecules targeting glycoprotein 120 [gp120; fostemsavir], monoclonal antibodies targeting CD4 [ibalizumab], capsid inhibitors [lenacapavir], the fusion inhibitor T-20 or other investigational agents).
- 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).
- INSTI 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 and/or in 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 therapeutic options (following multiple failing regimens, including INSTIs and CCR5 antagonists).

7.3 Individuals with no or limited drug resistance

Recommendations

- We recommend that factors associated with suboptimal adherence are considered for individuals experiencing virological failure on first-line ART with wild-type virus at baseline and without emergent resistance mutations at failure (GPP).
- If the current regimen is well tolerated and there are no concerning drug–drug interactions, it may be reasonable to continue the same regimen (GPP).
- If there are tolerability issues or significant drug–drug interactions, a switch in regimen should be considered (GPP).

Rationale

7.3.1 First-line treatment failure with no resistance

Seventy percent of individuals have wild-type virus despite failure of therapy [30-36]. Failure is usually attributable to poor treatment adherence with drug levels that are both insufficient to maintain viral load suppression and inadequate to select out viral mutations associated with drug resistance 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 with careful discussion with the individual. TDM may be of benefit to confirm low/absent therapeutic drug levels and to enable targeted discussion (see Section 6.2.4 TDM).

The absence of detectable resistance mutations does not exclude the presence of mutations in minor virus populations, especially with the NNRTIs [9,10,37]. This may increase the likelihood of subsequent failure if the same first-line drugs, or drugs in the same class, are prescribed [38,39]. Nevertheless, testing for minority resistance requires a specialist test and expert interpretation by a virologist is essential. There is no indication for routine testing for minority species for individuals with wild-type virus and failed therapy.

Following the development of virological failure, or persistent low-level viraemia, on either an NNRTI or first-generation INSTI-based ART regimen with two NRTIs and when no resistance mutations are detected, switching to a regimen with a higher-genetic barrier (such as a boosted PI or dolutegravir or bictegravir) may be optimal. 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 individual should be monitored carefully and repeat viral load testing performed after approximately 4 weeks. If there is an inadequate virological

response, resistance testing should be performed to detect any archived resistance. Switching to an NNRTI- or INSTI-based ART regimen is another option but must be individualised, including consideration of history of virological failure. In deciding which option to use, knowledge of the likely cause of virological failure (especially detailed reasons for poor adherence) is important. In an NNRTI/two-NRTI regimen, when all three agents have been stopped, the prevalence of NNRTI resistance is 12–16% depending on whether there is a simultaneous or staggered interruption [40,41].

7.3.2 First-line treatment failure with NNRTI resistance

Up to two-thirds of people living with HIV with virological failure on an NNRTI/two-NRTI ART combination harbour viruses with NNRTI resistance mutations and at least half have NRTI resistance mutations at 48 weeks [33-36,42]; with increasing time, accumulation of resistance mutations may compromise second-line regimens [43]. The finding of associated NRTI resistance is more frequent in individuals on a thymidine analogue backbone than in those on a non-thymidine analogue backbone. Although there are a number of potential options for second-line therapy after failure on an NNRTI-containing regimen, evidence supports one of three strategies:

- Dolutegravir plus two NRTIs. In the DAWNING study [REF], patients who experienced virological failure while on a first-line NNRTI-based regimen were randomly assigned to receive either a boosted PI (lopinavir/r) or dolutegravir; in addition two NRTIs were given, one of which had to be fully active based on resistance testing. The study was stopped after an interim analysis showed that the dolutegravir arm was superior to the lopinavir/ritonavir arm.

  In the NADIA study [REF], patients who experienced virological failure while on a first-line NNRTI-based regimen were randomly assigned to receive either darunavir/ritonavir or dolutegravir; in addition patients were randomly assigned to receive either zidovudine or tenofovir-DF in combination with lamivudine. Dolutegravir was found to be as effective as the boosted PI and tenofovir-DF was non-inferior to zidovudine as second-line therapy including in those with extensive NRTI resistance.

  Dolutegravir may be preferable to a boosted PI in terms of tolerability and fewer potential drug–drug interaction but it is worth noting that, although there was no difference in the rates of virological failure after switching between the two arms, four people in the dolutegravir arm developed dolutegravir resistance, associated with poor adherence, compared to none in the darunavir/ritonavir arm.

Commented [CNS296]: Michael Aboud, Richard Kaplan, Johannes Lombaard et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. Lancet 2019; 19: 253–264.

Commented [CNS297]: Paton NI, Musaazi J Kityo C et al. Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV. N Engl J Med 2021; 385(4):330-341.

Although bictegravir may have similar activity after first-line NNRTI failure, there have been no large clinical trials to demonstrate this in the context of detectable viraemia. First-line and suppressed switch trials have demonstrated efficacy when switching to bictegravir/tenofovir-AF/emtricitabine in the presence of historical NRTI mutations detected on genotypic RNA [REFS] and proviral DNA sequencing [REF]. It should be noted that the clinical implication of resistance mutations detected only in proviral DNA is not certain.

- A boosted PI plus two NRTIs. In addition to the NADIA study described above, three large randomised controlled trials [44-46] explored different strategies following first-line virological failure including a boosted PI plus NRTIs or a boosted PI plus raltegravir. These studies demonstrated non-inferiority between the two strategies described and also, interestingly, showed that NRTIs retained substantial virological activity. 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 although boosted darunavir may be better tolerated than other PIs.
- A boosted PI plus an INSTI. As described above, combining raltegravir with a boosted PI has been found to be as efficacious as a boosted PI regimen with at least two new or recycled NRTIs [44-46].

Sequencing from an efavirenz- or nevirapine-based regimen to etravirine is not recommended [47] unless switching to a new combination including a boosted PI. Switching to a first-generation INSTI (raltegravir or elvitegravir) or maraviroc with two active NRTIs is an option but is also not recommended if there are historical or existing reverse transcriptase mutations or previous virological failure on an NRTI-containing regimen [48].

7.3.3 First-line treatment failure on a ritonavir-boosted PI-based two-NRTI regimen with or without PI resistance

Less than 1% of individuals with virological failure harbour viruses with primary PI mutations and 10–20% have NRTI mutations at 48 weeks, with 75% having wild-type virus [30,33-35,49,50]. 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 viral load testing 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-, INSTI- or maraviroc-based regimen and again the decision should be individualised. Options include switching to a different boosted PI (darunavir/ritonavir is preferred unless resistance is

Commented [LW298]: Acosta RK, Willkom M, Andreatta K et al. Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) From Dolutegravir (DTG)+F/TAF or DTG+F/Tenofovir Disoproxil Fumarate (TDF) in the Presence of Pre-existing NRTI Resistance. J Acquir Immune Defic Syndr. 2020 Nov 1;85(3):363-371.
Hagins D, Kumar P, Saag M et al; BRAAVE2020 Investigators. Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide in Black Americans With HIV-1: A Randomized Phase 3b, Multicenter, Open-Label Study. J Acquir Immune Defic Syndr. 2021 Sep 1;88(1):86-95.

Commented [LW299]: Andreatta K, Willkom M, Martin R, C et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184V/I. J Antimicrob Chemother. 2019 Dec 1;74(12):3555-3564.

Commented [CNS300]: 44. Boyd MA, Kumarasamy N, Moore CL *et al.* Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet* 2013; **381**: 2091–2099.
45. Paton NI, Kityo C, Hoppe A *et al.* Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med* 2014; **371**: 234–247.
46. Amin J, Boyd MA, Kumarasamy N *et al.* Raltegravir non-inferior to nucleoside based regimens in second-line therapy with lopinavir/ritonavir over 96 weeks: a randomised open label study for the treatment of HIV-1 infection. *PLoS One* 2015; **10**: e0118228.

likely), a second-generation INSTI-based regimen or a different PI plus an INSTI. However, switching to a first-generation INSTI, 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 [48].

7.3.4 First-line treatment failure with first- and second-generation INSTI-based resistance

In studies of naïve subjects developing virological failure on raltegravir- or elvitegravir-containing regimens, up to 50% have been found to harbour viruses with primary integrase mutations and 25% have NRTI mutations at 48 weeks; approximately 50% have wild-type virus [32,42,49,51]. By contrast, resistance is extremely rare in studies in treatment-naïve individuals with dolutegravir or bictegravir/two-NRTI-based regimens [52-54]. Again, there are no existing clinical trial data to guide treatment decisions in the context of first-line INSTI failure but sequencing to a new regimen that includes a boosted PI is unlikely to lead to further emergent resistance and may be an option. 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 to include dolutegravir have shown that over 50% achieve a viral load <50 copies/mL [55] but, despite this, there are no data to support sequencing to dolutegravir after first-line failure. If considering the use of dolutegravir following virological failure with resistance to raltegravir or elvitegravir, twice daily dolutegravir is recommended. There are no data on the efficacy of bictegravir in patients who experience virological failure on a first-generation INSTI.

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 virological failure on an NRTI-containing regimen.

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 (or bictegravir) where success of response has been linked to the profile and number of resistance mutations.

7.4 Individuals with multi-class virological failure with or without extensive drug resistance

Recommendations

- We recommend that individuals with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed within a multidisciplinary team or referred for expert advice (GPP).
- We recommend that all past and current genotypic resistance test results and treatment history are reviewed in order to guide therapy decisions (GPP).
- We recommend that individuals with extensive drug resistance are switched to a new ART regimen containing at least two and preferably three fully active agents (Grade 1C).
- We suggest that consideration on an individual basis should be given to whether inclusion of NRTIs with predicted reduced activity on genotypic testing will provide additional antiviral activity (Grade 2C).
- Where there is extensive drug resistance, we recommend consideration of agents with novel mechanisms of action if available (GPP).
- We recommend consideration of clinical trials or expanded access programmes to facilitate the previous recommendation (GPP).
- We recommend that all individuals receive intensive adherence support at the start and at regular intervals to support them on their new ART combination (GPP).

Rationale

Until relatively recently, limited treatment options have been available for people living with HIV who have had virological failure with the three original classes of HIV ARV drugs (NRTIs, NNRTIs and PIs) and developed triple-class resistance. Most of these individuals have received prior suboptimal ARV treatment, often from the combination ART era in the mid-1990s, or have experienced adherence difficulties to multiple regimens and have accumulated resistance. However, with the introduction of INSTIs, particularly second-generation drugs, and newer inhibitors of reverse transcriptase and protease with enhanced activity against resistant virus as well as agents active through novel sites of action, even people with multi-class resistance can expect to achieve high levels of viral suppression [57,58].

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 extensive drug resistance with minimal treatment options and achieving viral suppression becomes increasingly difficult. The benefit of using resistance testing to guide ART choice for third-line regimens was demonstrated in ACTG A5288 [REF].

A non-inferiority trial comparing dolutegravir with raltegravir as the comparator included individuals with triple-class experience but who were naïve to INSTIs and had at least two-class resistance and at least one fully active drug as optimised background therapy [REF]. Overall, once-daily dolutegravir was superior to

Commented [LW301]: Grinsztejn B, Hughes MD, Ritz J et al; A5288 Team. Third-line antiretroviral therapy in low-income and middle-income countries (ACTG A5288): a prospective strategy study. Lancet HIV. 2019 Sep;6(9):e588-e600.

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raltegravir at 48 weeks in achieving a viral load <50 copies/mL. However, there was no benefit in individuals who had not received darunavir/ritonavir or had no primary darunavir mutations.

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

Recently, drugs with novel mechanisms of action have become licensed in the UK. These drugs include the first-in-class CD4 post-attachment inhibitor ibalizumab [REF] and the gp120-directed attachment inhibitor fostemsavir [REF]. The capsid maturation inhibitor lenacapavir [REF] has shown encouraging results in combination with other ARVs in heavily treatment-experienced patients and is also in late-stage development [REF].

A priority issue addressed by the writing group was the net contribution of recycling NRTIs in the context of virological failure and existing or potential reverse transcriptase mutations. In two studies including individuals previously naïve to ART for whom an NNRTI/two-NRTI regimen subsequently failed [REFS], a ritonavir-boosted PI 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 deferral of the introduction of drugs known to be active. However, NRTI inclusion was demonstrated to achieve improved virological control over ritonavir-boosted PI monotherapy up to 96 weeks [REF]. Maintenance of NRTIs even in the presence of extensive NRTI resistance is also supported by findings from both the DAWNING [REF] and NADIA [REF] studies. In particular, the NADIA study demonstrated that tenofovir-DF can be recycled following virological failure on a first-line tenofovir-DF-containing NNRTI-based regimen [REFS].

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 up to 48 weeks although there were three cases of virological failure in the simplification arm and none in the NRTI control arm [REF].

A further study included 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 [REF]. Following randomisation, subjects received the chosen regimen with or without the NRTIs.

Commented [CNS303]: Emu B, Fessel J, Schrader S et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1. N Engl J Med 2018; 379: 645–654.

Commented [CNS304]: Kozal M, Aberg J, Pialoux G et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. N Engl J Med 2020; 382:1232–1243.

Commented [CNS305]: Link, J.O., Rhee, M.S., Tse, W.C. *et al.* Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature* **584,** 614–618 (2020). https://doi.org/10.1038/s41586-020-2443-1

Commented [CNS306]: CROI 2022 – CAPELLA : Ogbuagu O et al. Long-acting lenacapavir in people with multidrug resistant HIV-1: week 52 results. CROI 2022. 12-16 February 2022, virtual. Poster abstract 491. https://www.croiconference.org/abstract/long-acting-lenacapavir-in-people-with-multidrug-resistant-hiv-1-week-52-results

Commented [CNS307]: 44. Boyd MA, Kumarasamy N, Moore CL *et al.* Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet* 2013; **381**: 2091–2099. 45. Paton NI, Kityo C, Hoppe A *et al.* Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med* 2014; **371**: 234–247.

Commented [CNS308]: 45. Paton NI, Kityo C, Hoppe A *et al.* Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med* 2014; **371**: 234–247.

Commented [CNS309]: As above:
Aboud et al. Lancet 2019
https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(19)30036-2.pdf
Paton et al. NEJM 2021

Commented [CNS310]: As above:
Paton et al. NEJM 2021
https://pubmed.ncbi.nlm.nih.gov/34289276/

Commented [CNS311]: Paton et al. NEJM 2021
https://pubmed.ncbi.nlm.nih.gov/34289276/

Commented [CNS312]: 71. Llibre J, Toro J, Clotet B *et al.* Withdrawing inactive NRTIs in subjects with suppressed viremia: a randomized trial. *Conference on Retroviruses and Opportunistic Infections*. Seattle, WA, USA. February 2015. Abstract 553.

Commented [CNS313]: 72. Gandhi RT, Tashima KT, Smeaton LM, et al. Long-term Outcomes in a Large Randomized Trial of HIV-1 Salvage Therapy: 96-Week Results of AIDS Clinical Trials Group A5241 (OPTIONS). J Infect Dis. 2020 Apr 7;221(9):1407-1415. .

The results demonstrated that 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.

An additional 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 [REFS]. Studies using lamivudine monotherapy for individuals developing therapy failure have shown that those harbouring M184V who continue on lamivudine maintain lower viral loads, have smaller declines in CD4 cell count, and rarely develop new reverse transcriptase mutations [REFS]. 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 [REFS]. Moreover, continuing lamivudine in conjunction with boosted PI therapy in second-line ART was associated with a high rate of success, despite the presence of M184V, when compared with boosted PI monotherapy [REF]. It is the recommendation of the writing group that maintenance of lamivudine/emtricitabine should be considered even in the presence of M184V.

For those drugs with a novel mode of action (fusion inhibitors and CCR5 antagonists), the absence of previous exposure indicates susceptibility, although maraviroc is only active against CCR5-tropic virus. For darunavir, tipranavir and etravirine, the number and type of mutations inform the degree to which these drugs are active [REFS]. The potential for drug–drug interactions is also important. Etravirine can be paired with darunavir/ritonavir (but not tipranavir/ritonavir or dolutegravir), and maraviroc dosing is variable depending on the other drugs in the new regimen.

Some individuals can have a successfully suppressive fully active three-drug regimen constructed without a boosted PI [REF]. Nevertheless, where feasible, a boosted PI such as darunavir/ritonavir should be included because of its protective effect on emergent resistance to the other drugs in the regimen. Darunavir/ritonavir can be given as 800/100 mg once daily in treatment-experienced individuals without darunavir resistance-associated mutations [REF].

The same principles regarding reviewing adherence, tolerability/toxicity issues, drug–drug and drug–food interactions, and mental health/drug dependency problems apply (see Box 7.1). 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 therefore careful discussion is important.

Commented [CNS314]: 73. Larder BA, Kemp SD and Harrigan PR. Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science* 1995; **269**: 696–699.
74. Quan Y, Brenner BG, Oliveira M and Wainberg MA. Lamivudine can exert a modest antiviral effect against human immunodeficiency virus type 1 containing the M184V mutation. *Antimicrob Agents Chemother* 2003; **47**: 747–754.

Commented [CNS315]: 75. Eron JJ, Benoit SL, Jemsek J *et al.* Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. North American HIV Working Party. *N Engl J Med* 1995; **333**: 1662–1669.
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Commented [CNS316]: 78. Wainberg MA, Miller MD, Quan Y *et al.* In vitro selection and characterization of HIV-1 with reduced susceptibility to PMPA. *Antivir Ther* 1999; **4**: 87–94.
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Commented [CNS317]: Ciaffi et al. Lancet HIV 2017https://pubmed.ncbi.nlm.nih.gov/28566227/

Commented [CNS318]: 80. Vingerhoets J, Peeters M, Azijn H *et al.* An update of the list of NNRTI mutations associated with decreased virologic response to etravirine (ETR): multivariate analyses on the pooled DUET -1 and DUET 2 clinical trial data. *XVII International Drug Resistance Workshop*. Sitges, Spain. June 2008. Abstract 24.
81. Lambert-Niclot S, Flandre P, Canestri A *et al.* Factors associated with the selection of mutations conferring resistance to protease inhibitors (PIs) in PI-experienced patients displaying treatment failure on darunavir. *Antimicrob Agents Chemother* 2008; **52**: 491–496.

Commented [CNS319]: 83. Nozza S, Galli L, Visco F *et al.* Raltegravir, maraviroc, etravirine: an effective protease inhibitor and nucleoside reverse transcriptase inhibitor-sparing regimen for salvage therapy in HIV-infected patients with triple-class experience. *AIDS* 2010; **24**: 924–928.

Commented [CNS320]: 84. Cahn P, Fourie J, Grinsztejn B *et al.* Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. *AIDS* 2011; **25**: 929–939.

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

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 be the case where it is difficult to construct a regimen with fully active drugs including a boosted PI (Grade 2C).
- We recommend against discontinuing or interrupting ART (Grade 1B).
- We recommend against adding a single, fully active ARV because of the risk of further resistance (Grade 1D).
- We recommend against the use of maraviroc to increase the CD4 cell count where there is evidence for X4- or dual-tropic virus (Grade 1C).
- 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 (Grade 1C).

Rationale

The use of currently available ARV drugs has resulted in a dramatic decline in the number of patients who have limited or no therapeutic options because of multi-class resistance or failure.

There is evidence from cohort studies that continuing therapy, even in the presence of viraemia and the absence of CD4 cell count increases, reduces the risk of disease progression [REFS] whereas interruption may lead to a rapid fall in CD4 cell count and a rise in viral load [REFS]. Evidence from other studies suggests continued immunological and clinical benefits if the HIV RNA level is maintained below approximately 10,000–20,000 copies/mL [REF]. Hence, if the CD4 cell count is well maintained (>200 cells/mm^3), there is an argument to continue the failing regimen and not change treatment until investigational agents are available to create a suppressive regimen. However, the potential benefit must be balanced against the ongoing risk of accumulating additional resistance mutations and the regimen should be maintained for the shortest period possible [REFS].

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.

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Commented [CNS323]: 90. Ledergerber B, Lundgren JD, Walker AS *et al.* Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet* 2004; **364**: 51–62.

Commented [CNS324]: 91. Kristiansen TB, Pedersen AG, Eugen-Olsen J *et al.* Genetic evolution of HIV in patients remaining on a stable HAART regimen despite insufficient viral suppression. *Scand J Infect Dis* 2005; **37**: 890–901.
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CD4 count <100 cells/mm^3) 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 [REF].

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. By contrast, in a meta-analysis, CCR5 receptor antagonists were not significantly associated with increases in CD4 cell count compared with other new drugs (*P*=0.22) [REF].

VIKING-3 [REF] was a study in 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; by day 8 and at the time of switching to an optimised background regimen, the mean drop in viral load was $\log_{10}$ 1.43. By week 24, 69% of participants had achieved a viral load <50 copies/mL. Response was associated with dolutegravir susceptibility and was most reduced in those with Q148 with at least two additional resistance mutations.

Ibalizumb is an injectable monoclonal antibody that is able to bind CD4 at a site that does not prevent its physiological function but is able to prevent HIV attachment. It is FDA approved for treatment of multidrug-resistant HIV. In the pivotal clinical study [REF], a single-arm, open-label Phase 3 trial in which ibalizumb was added to a failing regimen as a single agent, mean CD4 count was 150 cells/mm^3 and median viral load was 4.5 $\log_{10}$ copies/mL in participants at baseline. At week 25, the treated individuals had achieved a drop of 1.6 $\log_{10}$ copies/mL in viral load from baseline, with 50% below 200 copies/mL. The most common side effect was diarrhoea (in 20%). Among 10 individuals with virological failure, nine had evidence of virus that had reduced susceptibility to drug at failure compared to the baseline sample, indicating emergent resistance.

Fostemsavir is a prodrug of temsavir, an attachment inhibitor targeting HIV envelope (Env) gp120, that is independent of X4/R5 preference of Env. The randomised, placebo-controlled, Phase 3 BRIGHTE study [REF] enrolled 272 heavily experienced patients (viral load >400 copies/mL at screening) with fostemsavir or placebo added to the failing regimen. Fostemsavir was very well tolerated. After day 8, response rate was 54% in the fostemsavir group versus 38% in the placebo group. Further analyses demonstrate that certain env amino acid substitutions may be associated with reduced drug susceptibility. Fostemsavir is a possible candidate drug for use with at least one other fully active agent. Treatment-emergent mutations occurred in almost half of patients with virological failure following fostemsavir treatment.

Commented [CNS325]: 93. Murray JS, Elashoff MR, Iacono-Connors LC *et al.* The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS* 1999; **13**: 797–804.

Commented [CNS326]: 69. Pichenot M, Deuffic-Burban S, Cuzin L and Yazdanpanah Y. Efficacy of new antiretroviral drugs in treatment-experienced HIV-infected patients: a systematic review and meta-analysis of recent randomized controlled trials. *HIV Med* 2012; **13**: 148–155.

Commented [CNS327]: 55. Castagna A, Maggiolo F, Penco G *et al.* Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. *J Infect Dis* 2014; **210**: 354–362.

Commented [CNS328]: Emu B, Fessel J, Schrader S et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1. N Engl J Med 2018; 379: 645–654.

Commented [CNS329]: Kozal M, Aberg J, Pialoux G et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. N Engl J Med 2020; 382:1232–1243.

The capsid inhibitor lenacapavir was studied in injectable form in a recent small randomised study (*n*=36) in heavily treatment-experienced patients with three-class resistance and viral load >400 copies/mL [REF]. In this study lenacapavir was added to an optimised background regimen, and participants (median 24 years since HIV diagnosis) had received a median of 11 previous agents. The favourable pharmacokinetic properties of lenacapavir allow for potential oral single dosing over 6 months, although subcutaneous injection was used in the trial. The drug targets a highly conserved region in p24, and therefore all subtypes appear susceptible.

Commented [CNS330]: CROI 2022 – CAPELLA : Ogbuagu O et al. Long-acting lenacapavir in people with multidrug resistant HIV-1: week 52 results. CROI 2022. 12-16 February 2022, virtual. Poster abstract 491. https://www.croiconference.org/abstract/long-acting-lenacapavir-in-people-with-multidrug-resistant-hiv-1-week-52-results

Where lenacapavir is not available, and there are no other fully active drugs, we recommend use of both attachment inhibitors in combination (expert opinion).

Finally, where feasible, people living with HIV should be given the opportunity to enrol in research studies or expanded access programmes evaluating investigational new drugs. Drugs developed for, and used in, other settings (such as pegylated interferon) that have been incidentally demonstrated to decrease viral load should not be used without discussion with experienced HIV physicians in a multidisciplinary team because data are either too limited or contradictory.

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8 Specific populations

This section provides guidance and recommendations for the treatment of specific populations with HIV.

TB/HIV co-infection: guidance and recommendations regarding prescribing ART in individuals with HIV co-infected with TB can be found in the BHIVA guidelines for the management of tuberculosis in adults living with HIV 2018 (https://www.bhiva.org/TB-guidelines).

Hepatitis B or C/HIV co-infection: guidance and recommendations regarding prescribing ART in individuals with HIV co-infected with hepatitis B or hepatitis C can be found in the BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV 2013 (https://www.bhiva.org/hepatitis-guidelines).

HIV-related cancers: details about HIV-related cancers and prescribing ART for people with HIV and these cancers can be found in the BHIVA guidelines for HIV-associated malignancies 2014 (www.bhiva.org/malignancy-guidelines.aspx).

8.1 HIV-associated cognitive impairment

8.1.1 Introduction

With the widespread use of effective combination ART, the incidence of severe HIV-associated cerebral disease has declined dramatically [1]; however, more subtle forms of brain disease, known as HIV-associated cognitive disorders, are reported to remain prevalent [2]. This cognitive 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 (i.e. the cortical defect typical of Alzheimer's disease [3]).

Studies describing prevalence of HIV-associated cognitive impairment vary depending on definitions used and populations studied [5-7]. Cohorts including only aviraemic and symptomatic subjects suggest the prevalence of cognitive impairment to be between 6% and 19% [6,8-10]. Risk factors for the development of cognitive disorders are poorly understood and are likely to be multifactorial including both HIV disease-related factors [11,12] and concomitant non-HIV-related factors, particularly multimorbidity and polypharmacy associated with ageing [13-17]. Although it is possible that the choice of combination ART that subjects receive may influence cognitive function, this is a controversial area without definitive evidence. The following recommendations apply to individuals with symptomatic HIV-associated cognitive disorders.

8.1.2 When to start ART

Recommendation

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

Rationale

Current evidence suggests that cognitive function improves after commencing ART for the first time [18] in both cognitively symptomatic [19] and asymptomatic [20] subjects. However, these studies have been undertaken in individuals with other indications to commence ART, in general with CD4 cell counts <350 cells/mm^3. A neurology substudy of START did not demonstrate cognitive benefits in patients immediately commencing ART; however, potential benefits may have been confounded by the high rates of efavirenz-based ART [21]. Early ART after HIV acquisition may be associated with lower rates of cognitive impairment that are comparable to rates in HIV-negative populations [22,23]. For vulnerable individuals, the possible advantages to brain health of successful early HIV suppression must be balanced against ensuring ART adherence, a key determinant of long-term cognitive outcomes.

8.1.3 What to start

Recommendations

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

Rationale

8.1.3.1 Including zidovudine in a regimen

During the earlier years of ART, clear benefits on cerebral function of individual ARV drugs such as high-dose zidovudine were reported [24] and the benefits of combination therapy overall described [18], however data are sparse regarding any differences in these benefits between individual agents or combinations. Within cohort studies, the use of NRTIs within ART regimens has been associated with a reduced risk of severe HIV-associated dementia [25] compared to the use of other regimens; however, the confounders of a cohort study limit the interpretation of these data. The improvements in cognitive function observed with zidovudine monotherapy [24] and the greater improvements in cognitive function observed with a zidovudine-containing quadruple NRTI regimen compared to other ART regimens [26] raise the possibility of

selecting a zidovudine-containing regimen in subjects with cognitive impairment. Conversely, a lack of comparator data for zidovudine monotherapy, and potential toxicities arising from zidovudine use, may limit the relevance of these data [27].

8.1.3.2 Clinical penetration effectiveness score

Attempts have been made to establish a relationship between cognitive function and CNS ARV drug delivery based on an ARV scoring system known as the clinical penetration effectiveness (CPE) score [28]. The CPE score aims to rationally rank the cerebral effects of individual ARV agents. However, the system is predominantly based on pharmacokinetic modelling rather than pharmacodynamic endpoints such as data describing changes in cognitive function. Studies that have assessed the correlation between the CPE scores of ART regimens and cognitive function report conflicting findings with some cohorts showing a positive association [29,30] whereas other cohorts describe a negative association [31,32]. In a small prospective study, no differences in cognitive outcomes were observed in subjects randomly assigned to higher CPE score-containing ART regimens compared to standard therapies [9]. Given these factors, the CPE score should not influence therapeutic decisions in subjects with cognitive impairment commencing ART.

8.1.3.3 Neurotoxicities of ARVs

Although early neuropsychiatric side effects are widely recognised and common with efavirenz-containing therapy, recent reports have highlighted concerns regarding poorer cognitive function being associated with efavirenz-containing regimens. In one cohort study, poorer cognitive function was found to be associated with current efavirenz use [33]. Two randomised controlled studies have assessed the cognitive effects of efavirenz [26,34]. In one small study, improvements in cognitive function were poorer in those allocated to efavirenz-containing therapy [26] and in a large study, the time to development of cognitive impairment was reduced in subjects allocated to efavirenz-containing therapy [34]. ARV switch studies have reported improvement in CNS symptomatology when modifying therapy to non-efavirenz-containing regimens [35,36]. We recommend avoiding efavirenz in individuals with baseline cognitive impairment or mental health, and switching individuals who develop symptoms while on efavirenz-containing regimens.

Post-licensing cohort studies of INSTIs have reported neuropsychiatric side effects in specific at-risk populations (such as older individuals or those with pre-existing mental health morbidity) which may have been missing from the original licensing trials [37]. Neurotoxicities associated with INSTIs are predominantly reported as insomnia and anxiety rather than cognitive impairment. At present, there are insufficient data to support avoiding INSTI-based regimens in individuals with symptomatic cognitive disorders, particularly given the high efficacy and low pill burden of many modern regimens, however vigilance is advised.

8.1.4 Simplification strategies

Recommendation

- We recommend avoiding dual therapy regimens in individuals with HIV-associated cognitive disorders (Grade (1C).

Rationale

Novel ARV strategies, particularly dual therapy with INSTIs or PIs, continue to be of interest given the potential for reduced long-term toxicities. Concerns have been raised regarding the cerebral effects of both PI monotherapy [38] and dual therapies [39].

Such concerns are based on the hypothesis that novel strategies comprise only one or two effective ARV agents that may not adequately suppress ongoing HIV replication in sanctuary sites such as the CNS [28]. Isolated cases describing the evolution of CNS disease in previously stable people living with HIV receiving PI monotherapy have been reported [40]. In the PIVOT study, the largest study of PI monotherapy, no differences in parameters of cognitive function were noted over 5 years of follow-up in subjects randomly assigned to continue standard therapy versus commence PI monotherapy [41]. Similarly reassuring data were reported during shorter follow-up of PI dual therapy [42,43]. However, all PI monotherapy studies recruited low numbers of neurologically symptomatic subjects. Subsequent, large cross-sectional and prospective studies of aviraemic individuals found an association between HIV CSF escape and PI use [44,45]. However, the prevalence of CSF escape was low and did not correlate with cognitive function at the single timepoint of analysis [44].

In a retrospective cohort study of aviraemic individuals at high risk or with symptoms of cognitive impairment, no differences in CSF escape or cognitive function were identified between individuals receiving a range of dual therapy regimens compared to those receiving standard triple therapy [46]. However INSTI-containing regimens were predominantly used in the small and heterogenous dual therapy group.

There are few data describing efficacy and safety of modern dual regimens in the CNS. In one open-label study, virologically suppressed individuals switching to dolutegravir-based dual therapy experienced more neuropsychiatric adverse events leading to discontinuation compared to those receiving standard triple therapy [47]. In another open-label switch study, discontinuation rates were comparable between dolutegravir-based dual therapy and triple therapy arms despite higher rates of insomnia reported in the dual therapy group [48]. No cognitive adverse events were identified in the first 48 weeks of either study and the populations studied were relatively young with a median age of less than 50 years. Randomised

controlled clinical trials to study long-term safety and efficacy of simplified regimens in the CNS and other compartments in naïve and experienced patients are awaited.

Long-acting injectable therapies represent a particularly attractive treatment for those individuals at risk of or with established cognitive impairment by removing the daily pill burden. In the only available study of injectable therapy in virologically suppressed individuals, who also had no history of treatment failure, no significant neuropsychiatric or cognitive adverse events were reported in either injectable or oral therapy arms [49].

8.1.5 Continuing or worsening cognitive impairment despite ART

Recommendations

Best practice management should include (GPP):

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

Rationale

Several randomised controlled studies, assessing both intensification of ART with new ARV agents [9,50] and with adjunctive therapies [51-54] have been published. Unfortunately, none of these studies describes improvements in cognition subsequent to the study interventions. In one small, randomised, open-label pilot trial of symptomatic patients, switching from a dolutegravir-containing to elvitegravir-containing regimen improved neuropsychiatric and cognitive outcomes [55]. However, there are insufficient data to recommend switching between INSTIs in individuals who develop cognitive symptoms while on INSTI-containing triple therapy regimens. No benefit on cognitive function have been observed in a study assessing ART intensification with maraviroc and/or dolutegravir (NCT02519777) [56]. Without evidence-based interventions, a best-practice approach based on the current literature is outlined. As HIV-associated cognitive disorders are diagnoses of exclusion, re-evaluation of subjects with ongoing cognitive impairment despite ART for confounding conditions is recommended, with expert input from other clinical specialties such as psychiatry, neurology and neuropsychology and where possible from an HIV neurology service. Given the presence of non-infectious comorbidities reported to be a risk factor for cognitive impairment [13], 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 people with ongoing cognitive impairment for two reasons. First, data from cohorts of untreated people living with HIV would suggest that CSF HIV RNA levels are higher in those with HIV-associated dementia and cognitive decline [57-59] and therefore suppression of CSF HIV RNA may be beneficial for cognitive function. Secondly, in people with ongoing cognitive impairment, higher degrees of genetic diversity between HIV viral strains in the CSF and plasma compartment may exist [60], even in those with undetectable plasma HIV RNA [4,61]. Therefore, assessment for CSF HIV resistance is justified in order to tailor ART. Management should also involve consideration of any potential toxicities and side effects of ARV drugs. For instance, a trial of switching from an efavirenz-containing to an alternative regimen may be considered along with any potential disadvantages of treatment modifications as outlined above.

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8.2 Chronic kidney disease

8.2.1 What to start

Recommendations

- We recommend darunavir/ritonavir in individuals with an eGFR of <60 mL/min/1.73 m^2 if a PI is required (Grade 1C).
- We recommend tenofovir-AF in individuals with eGFR 30–60 mL/min/1.73 m^2 who require tenofovir (Grade 1B).

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 [1,2]. Renal impairment and proteinuria are powerful predictors of kidney disease progression [3-5]. Therefore, ART with nephrotoxic potential (tenofovir-DF [6-9], lopinavir/ritonavir [10] and atazanavir [10,11]) is best avoided in individuals with an eGFR of (or approaching) <60 mL/min/1.73 m^2, or moderate-to-severe proteinuria (urine protein-to-creatinine ratio >50 mg/mmol or urine albumin-to-creatinine ratio >30 mg/mmol).

The use of tenofovir-DF and tenofovir-AF (each co-administered with emtricitabine, elvitegravir and cobicistat) has been compared in two randomised controlled clinical trials of ART-naïve persons with eGFR >50 mL/min/1.73 m^2. At 3 years, there were significantly more renal discontinuations in the tenofovir-DF arm (12 *vs* 0; *P*<0.001) [12].

The relative safety of tenofovir-AF has also been demonstrated in individuals with CKD (eGFR 30–70 mL/min/1.73 m^2), with marked reductions in tubular proteinuria within days of switching from tenofovir-DF to tenofovir-AF, and stable eGFR over 96 weeks [13].

8.2.2 Need to switch

Recommendation

- We recommend against continued use of tenofovir-DF, lopinavir/ritonavir or atazanavir in individuals with worsening renal function who have developed or are approaching an eGFR <60 mL/min/1.73 m^2 or who have developed moderate-to-severe proteinuria, if acceptable alternatives are available (Grade 1C).

Rationale

Tenofovir-DF may cause renal tubular injury and proximal tubulopathy [9,14]. Tenofovir-DF has been associated with eGFR decline, CKD and proteinuria in cohort studies [10,11,15], and discontinuation of tenofovir-DF with improved kidney function [16,17]. Tenofovir-AF has an improved renal safety profile, with stable eGFR patterns in those with renal impairment (eGFR 30–70 mL/min/1.73 m^2) [13], reductions in (tubular) proteinuria [13,18] and a lower incidence of renal discontinuations and no reported cases of proximal tubulopathy in clinical trials [18,19].

Atazanavir may cause kidney stones or tubulo-interstitial nephritis [8,20-23]. Atazanavir and lopinavir/ritonavir, but not darunavir, have been associated with CKD and eGFR decline in cohort studies [10,24,25], and switching from atazanavir or lopinavir/ritonavir to darunavir has been associated with improved renal function [26].

The optimal treatments for people with severe CKD (stage 4 CKD: eGFR 15–29 mL/min/1.73 m^2) and end-stage kidney disease (ESKD; dialysis or transplantation) remain to be defined [27]. In individuals with stage 4 CKD, tenofovir-AF (25 mg) results in 5- to 6-fold higher tenofovir exposures as compared to individuals with normal kidney function (similar to tenofovir exposures with tenofovir-DF as part of unboosted regimens in people with normal kidney function) [28]. If tenofovir-AF is required to suppress HIV and/or hepatitis B in people with severe CKD, an unboosted third agent together with tenofovir-AF/emtricitabine (10/200 mg once daily) could be considered with careful monitoring for worsening kidney function and proximal tubulopathy, although there are no data to support such a strategy.

Transplantation is the preferred treatment modality for ESKD [29]. Hence, ART regimens for people with ESKD should be optimised for the post-transplant setting in which impaired renal function, eGFR decline, proteinuria, acute kidney injury and drug–drug interactions between ART and calcineurin inhibitors (tacrolimus and ciclosporin) are common [27]. Tenofovir-AF/emtricitabine/elvitegravir/cobicistat (administered once daily; *n*=55) and tenofovir-AF/emtricitabine/bictegravir (once daily; *n*=10) are the only ART regimens that have been formally studied in people on dialysis [30,31]. Although most participants maintained viral suppression on these regimens, tenofovir exposures were almost 30-fold and 2- to 4-fold higher than those achieved with tenofovir-AF and tenofovir-DF, respectively, in people with normal kidney function; the effects of these high exposures on residual kidney function and bone are unknown. For people on dialysis, we recommend the use of ART regimens that are optimised for use in kidney transplantation; such regimens should not include cobicistat or ritonavir, and tenofovir-AF should be avoided unless individuals are hepatitis B surface antigen positive or require tenofovir to maintain viral suppression.

The advent of two-drug regimens such as dolutegravir/lamivudine and dolutegravir/rilpivirine has provided more options to manage HIV in the setting of renal impairment and/or moderate-to-severe proteinuria. However, experience with these regimens is still limited [32].

8.2.3 Dose adjustment of ART in the setting of renal impairment

Recommendation

- We suggest that lamivudine and emtricitabine are dose adjusted in people with a confirmed eGFR of <30 mL/min/1.73 m^2 (GPP).

Rationale

All currently licensed NRTIs (except abacavir) are renally cleared [33]. Hence, exposures of most NRTIs increase in renal impairment, and progressive dose reductions are recommended as renal function declines [34]. As HIV treatment guidelines evolved, dose reductions have remained relevant for a few ARVs, most notably emtricitabine, lamivudine and tenofovir. Full-dose (200 mg daily) emtricitabine has been studied in people with renal impairment (eGFR 30–70 mL/min/1.73 m^2) and in people on dialysis; although plasma exposures were predictably elevated, no toxicity signal was detected [30,35]. The same is probably true for lamivudine: full-dose (300 mg daily) lamivudine appears to be safe in people with eGFR >30 mL/min/1.73 m^2 [36,37], and 100–150 mg daily in those on haemodialysis [36]. These data provide support for continued use of fixed-dose, emtricitabine- or lamivudine-containing ART combinations in individuals with mild-to-moderate renal impairment. Clinicians need to avoid unnecessary dose reduction of emtricitabine or lamivudine where these agents are co-administered with dolutegravir or other agents that have major effects on tubular creatinine secretion (which leads to overestimation of the severity of renal impairment) [33]. As described above (see Section 8.2.2 Need to switch), tenofovir-DF should be avoided in people with eGFR <60 mL/min/1.73 m^2 or rapid eGFR decline, and tenofovir-AF should be avoided in those with eGFR <30 mL/min/1.73 m^2. Intermittent dosing is well established for tenofovir-DF [34]; there are no data for intermittent dosing of tenofovir-AF.

8.2.4 Assessment of renal function in the presence of agents that reduce creatinine clearance

Recommendations

- We suggest that repeat and additional measures of kidney function (eGFR and urine protein-to-creatinine ratio) are obtained if large reductions in eGFR are observed following the introduction of drugs that inhibit tubular creatinine secretion (GPP).

- We suggest that an alternative estimate of eGFR (e.g. based on cystatin C) is obtained in individuals in whom reductions in creatinine-based eGFR on drugs that inhibit tubular creatinine secretion may affect decisions about dose reduction or substitution of medications (GPP).

Rationale

Several ARV drugs, including dolutegravir, bictegravir, raltegravir, doravirine, rilpivirine, ritonavir and cobicistat, inhibit tubular secretion of creatinine, resulting in modest elevations of serum creatinine concentrations. These benign effects are mediated by inhibition of creatinine transporters on the apical or basolateral membrane of the tubular cells and are not accompanied by new-onset or worsening proteinuria, haematuria or glycosuria. Moreover, the inhibitory effects on creatinine secretion are fully established by 2–4 weeks, and reversible upon discontinuation of the relevant agent(s) [33]. The increase in serum creatinine concentrations affects eGFR or creatinine clearance; large reductions in eGFR may be observed in people with normal renal function [38]. If this benign effect of these ARV drugs is not recognised, tenofovir toxicity may be inadvertently diagnosed or renally cleared medications inadvertently dose reduced. Repeat and/or alternative measures of renal function (e.g. cystatin C and urinalysis) can help to distinguish benign effects of ART on creatinine secretion from renal injury [38].

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8.3 Cardiovascular and metabolic disease

8.3.1 Cardiovascular considerations

Recommendations

In individuals with high CVD risk:

- We recommend avoiding lopinavir/ritonavir-based regimens (Grade 1C).
- If a boosted PI is the desired option, an atazanavir-based regimen may have advantages over a darunavir-based regimen (GPP).
- We suggest avoiding abacavir (Grade 2C).

Rationale

CVD has been recognised for many years as a significant contributor to morbidity and mortality in people living with HIV. The prevalence of CVD is high in people living with HIV with the onset at a younger age than in the HIV-negative population. A recent meta-analysis which included over 700,000 people living with HIV estimated a relative risk of CVD of 2.16 in people living with HIV compared to those without HIV [1].

For the purposes of these guidelines, an elevated CVD risk is defined as: established atherosclerotic CVD; diabetes mellitus type 1 over the age of 40 years; an eGFR of <60 mL/min/1.73 m^2 and/or albuminuria; familial hypercholesterolaemia; and/or a high calculated CVD risk [2].

In some studies, specific ARV agents have been associated with CVD. Current abacavir use has been associated with myocardial infarction risk in multiple observational studies [3], leading to our recommendation of alternative ARV options for individuals with established or risk factors for CVD. Cumulative exposure to several of the PIs has been associated with increased risk of myocardial infarction,

including more recently darunavir [4]. Such effects have not been observed to date with boosted or unboosted atazanavir [4, REFS]. Other cohorts have failed to show an association between darunavir exposure and CVD [REFS].

While CVD concerns exist for specific ARV drugs and classes, these concerns are clearly outweighed by the enormously beneficial effects of ART and viral suppression on reducing the overall incidence of CVD, with studies reporting a substantial reduction in risk of myocardial infarction in those virally suppressed [5].

8.3.2 Lipid considerations

Recommendation

- We recommend that the adverse effects on lipid parameters should be considered when selecting ART (GPP).

Rationale

The following ARV drugs are associated with dyslipidaemia:

- Boosted PIs
- Efavirenz
- Elvitegravir/cobicistat

Tenofovir-DF is associated with an improved lipid profile.

For many years, dyslipidaemia has been associated with both HIV disease and ART. Boosted PIs and the boosted INSTI elvitegravir affect serum lipid concentrations as does the NNRTI efavirenz [6].

Conversely, the NRTI tenofovir-DF was associated with beneficial effects on overall lipid profiles in healthy volunteer studies [7], when used for PrEP [8] and compared to the NRTIs abacavir [9] and tenofovir-AF [10] in randomised trials. Switch from tenofovir-DF to tenofovir-AF was associated with a deterioration in lipid parameters in both randomised trials [11] and cohort studies [12-14]. Lipid changes in the GS-1489 study were similar in the abacavir/lamivudine/dolutegravir and tenofovir-AF/emtricitabine/bictegravir arms suggesting that tenofovir-AF has a similar impact on lipids as abacavir [15]. There is insufficient evidence to suggest that overall CVD risk profile differs between tenofovir-DF and tenofovir-AF [16].

8.3.3 Weight gain considerations

Recommendation

- We recommend that the impact of weight gain should be considered when selecting ART (GPP).

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Rationale

In recent studies, the following ARV drugs have been associated with greater weight gain compared to comparator agents:

- Tenofovir-AF compared to tenofovir-DF or abacavir
- INSTI-containing regimens compared to NNRTI- or boosted PI-based regimens

Recently, in ART-naïve individuals, the initiation of INSTI-containing ART has been associated with greater weight gain than with the initiation of NNRTI- or boosted-PI-containing regimens [17-19]. In a recent pooled analysis of eight randomised controlled trials of around 5000 people with HIV initiating ART, those commencing an INSTI-containing regimen were more likely to have experienced significant weight gain after 2 years with the greatest effects observed with bictegravir and dolutegravir [20]. A similar pooled analysis of 12 suppressed switch trials reported that moderate post-switch weight gain was frequently observed and associated with younger age and lower baseline BMI; switch from efavirenz or rilpivirine to elvitegravir/cobicistat and tenofovir-DF to tenofovir-AF were associated with greatest risk of weight gain and switch from abacavir to tenofovir-AF was associated with less weight gain than switch from tenofovir-DF [21].

Tenofovir-AF has also been associated with greater weight gain when compared to tenofovir-DF in first-line studies, most markedly in black women [17]. Additionally, switching from tenofovir-DF to tenofovir-AF was associated with a weight gain of approximately 2 kg at 1 year in two large cohorts [14,22] and a randomised trial [23]. This may, in part, be explained by the abrogation of weight loss observed on tenofovir-DF, best demonstrated in PrEP trials [24], though this is non-progressive and typically less than 1 kg. Efavirenz has also been associated with relative weight loss which appears to be related to drug exposure [25]. Data from a randomised trial in pregnant women showed that weight gain was less than recommended in pregnancy but closest to normal for tenofovir-AF/emtricitabine/dolutegravir compared to tenofovir-DF/emtricitabine/dolutegravir and tenofovir-DF/emtricitabine/efavirenz [17,26].

The mechanisms underlying this weight gain remain unclear and the clinical implications of ART-associated weight change are uncertain. There is no evidence at present to support switching ART to manage weight gain though trials are ongoing or planned.

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8.4 Women

8.4.1 Introduction

The following guidance considers issues concerning the initiation and choice of ART for women with HIV who are not currently pregnant. For guidance on the management of pregnancy in women with HIV, please refer to the BHIVA guidelines for the management of HIV in pregnancy and postpartum [1]. Specific data on ART in women other than in pregnancy are limited. Available data are largely from meta-analyses or *post hoc* analyses or derived from cohort studies. Most of the randomised clinical trial data on ART are from studies that have enrolled mainly men. If randomised controlled trials do enrol women, the numbers are often too small to draw significant sex-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 women with HIV. Many women with HIV in the UK are of African heritage and face overlapping challenges to their health and wellbeing [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.

8.4.2 What to start

Recommendations

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

Rationale

8.4.2.1 Efficacy

There are few data to guide prescribing of initial ART specifically for women as no randomised controlled trial in people living with HIV starting ART has been powered to detect sex-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 was a women-only randomised controlled trial that demonstrated superiority of tenofovir-DF/emtricitabine/elvitegravir/cobicistat over tenofovir-DF/emtricitabine + atazanavir/ritonavir; this was driven predominantly by more adverse event discontinuations in the atazanavir arm [4]. A meta-analysis of FDA registrational randomised controlled trials analysed data from 20,328 individuals with HIV participating in 40 trials investigating 16 ARV agents. 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 [5].

In a study comparing atazanavir/ritonavir and efavirenz in 1857 ART-naïve individuals of whom 17% were women, female sex was associated with increased virological failure on atazanavir/ritonavir compared with efavirenz [6]. 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 treatment-experienced individuals [7]. 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 sex differences [8,9]. Cohort studies in the UK have reported similar virological outcomes during the first year of treatment in heterosexual men and women [10]. An Italian cohort study reported no significant effect of sex on clinical progression or the risk of developing a clinical event [11]. Data from Spain, which included both treatment-naïve and treatment-experienced women, showed similar virological responses compared to men [12].

8.4.2.2 Toxicity, discontinuation and adherence

Several studies have suggested that sex may influence the frequency, presentation and severity of selected ART-related adverse events. Although data are limited, there is evidence that the pharmacokinetic parameters of some ARV drugs may differ between men and women because of factors such as body weight, plasma volume, plasma protein levels, CYP450 activity and drug transporter function [13,14]. Adverse events and treatment discontinuations within ART clinical trials and cohort studies published between 2002 and 2007 have been systematically reviewed [15]. It was found that 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 [15]. Data from the USA have shown that women are more likely than men to discontinue ART because of poor adherence, dermatological symptoms, neurological reasons, constitutional symptoms and concurrent medical conditions [14]. UK cohort data showed 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) [10]. 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 [16]. In the UK population, this is of particular relevance to women with HIV, the majority of whom are of African heritage.

Compared with men with HIV, women are more likely to experience an increase in central fat with ART [17]. A retrospective study of over 1000 women followed up in the Women's Interagency HIV study from 2006 to 2011 compared virologically suppressed women who switched to a regimen containing an INSTI compared to those who did not. Overall, 73% were overweight or obese but a significant increase in glycated haemoglobin ($P \leq 0.0318$) and systolic ($P \leq 0.0191$) and diastolic ($P \leq 0.0121$) blood pressure were seen in those who switched to an INSTI-containing regimen [18]. Women have an increased risk of osteopenia/osteoporosis, especially after menopause, and this risk may be exacerbated by HIV and ART [19]. At present, these observed differences do not require women-specific recommendations. A systematic review of studies on sex and ART adherence published between 2000 and 2011 in resource-rich countries concluded that overall reported adherence is lower in women than men [20]. However, of over 1000 studies initially identified for review, only 44 had adequate data on sex to allow any comparisons to be made. The authors identified specific factors for lower adherence in women: depression, lack of supportive interpersonal relationships, young age, drug and alcohol use, black ethnicity, ART with six or more pills per day, higher numbers of children, self-perception of abdominal fat gain, sleep disturbances and increased levels of distress.

8.4.2.3 Fetal safety

All women of childbearing potential should be offered reproductive health counselling including advice around conception, prevention of vertical transmission and contraception as a component of routine medical care [21]. Concerns about potential fetal toxicity of ARV agents have influenced prescribing practice in women with HIV. 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. 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 found no differences in risk of detectable viral load at delivery, vertical transmission or congenital abnormality when comparing pregnancies that were managed with zidovudine-containing versus zidovudine-sparing ART [22]. The most robust data on teratogenicity and first trimester ART exposure are from the Antiretroviral Pregnancy Registry (APR) [23]. This international prospective reporting system records rates of congenital birth defects in babies born to women with exposure to ART during the first trimester. Approximately 200 reports need to be received for a particular compound before data are reported by the APR. An interim report was released in July 2020. There have been sufficient numbers of first trimester exposures of abacavir, atazanavir, efavirenz, emtricitabine,

lamivudine, lopinavir, nevirapine, ritonavir, tenofovir-DF and zidovudine to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes (i.e. cardiovascular and genitourinary systems). However, no such increases have been detected to date. A greater than 2-fold increase in overall birth defects has not been seen for cobicistat, darunavir, dolutegravir, elvitegravir, raltegravir, rilpivirine or tenofovir-AF.

Despite the APR report on dolutegravir [23], further analysis reported in 2020 from the Tsepamo study in Botswana has shown a rate of neural tube defects of 0.11% in women who conceived on dolutegravir-containing ART compared to 0.07% in women conceiving with an efavirenz-containing regimen [24]. Data from the IMPAACT study comparing dolutegravir + emtricitabine/tenofovir-AF versus dolutegravir + emtricitabine/tenofovir-DF versus efavirenz/emtricitabine/tenofovir-DF after the first trimester reported pregnancy outcomes in 640 women. There were fewer adverse outcomes in women in the dolutegravir + emtricitabine/tenofovir-AF arm (24.1%) compared to the dolutegravir + emtricitabine/tenofovir-DF (32.9%; *P*=0.043) and efavirenz/emtricitabine/tenofovir-DF (32.7%; *P*=0.047) arms [25].

There are insufficient data to recommend bictegravir, doravirine and cabotegravir/rilpivirine use during pregnancy.

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 ART regimen. Further details can be found in the BHIVA guidelines for the management of HIV in pregnancy and postpartum [1].

8.4.2.4 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 and hormone-replacement therapy. We suggest prescribers refer to the summary of product characteristics for individual drugs or the University of Liverpool HIV drug interactions website [26], or seek specialist pharmacy advice within their unit/network.

8.4.2.5 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, drug interactions with hormone-replacement therapy and increased risk of comorbidities such as CVD 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 premenopausal

and postmenopausal women in a US study found no significant differences in the immunological and virological responses between the two groups [27].

8.4.3 Women living with HIV experiencing virological failure

There is very little evidence to guide prescribing ART in women with HIV experiencing virological failure on ART, with women accounting for approximately 10% of those recruited in most studies. One study investigating darunavir/ritonavir 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 study 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 [28]. A further study has reported similar efficacy and tolerability of raltegravir in ART-experienced women with HIV [7]. In women with HIV experiencing virological failure on ART, the same principles of management and recommendations apply as for men with HIV experiencing virological failure.

8.4.4 Psychosocial issues

Women living with HIV often experience additional vulnerability factors (psychological and social) that can affect access to and engagement with care as well as adherence and treatment outcomes. Such factors include HIV-related stigma, low socioeconomic 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.

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8.5 Mental health

Recommendations

- 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 (Grade 1C).
- We recommend that INSTI-containing regimens should be used with caution in patients with a pre-existing history of any psychiatric illness including depression (GPP).

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 people living with HIV [2]. 'Suicidality' was defined as suicidal ideation or attempted or completed suicide. The

incidence of suicidality was 8/1000 patient-years (PY) with efavirenz versus 4/1000 PY without (hazard ratio [HR] 2.3; *P*=0.006); rates of attempted or completed suicide were 3/1000 PY versus 1/1000 PY respectively (HR 2.6; *P*=0.065) (eight suicides on efavirenz *vs* 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 9/1000 PY and 5/1000 PY on efavirenz and comparator regimens respectively (HR 2.06; *P*=0.007). Incidence of suicidality did not change during the period of follow-up indicating that risk could emerge at any time.

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 using data from the US FDA Adverse Event Reporting System (i.e. post-marketing surveillance data of spontaneous adverse event reports from people living with HIV and healthcare workers) explored the ratio of observed to expected numbers 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. The authors 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, whereas 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 ranks among the most adverse possible effects of any treatment. Unfortunately, depression is under-recognised by people living with HIV 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.

Neuropsychiatric side effects, including insomnia, anxiety and worsening depressive symptoms, have been reported for all INSTIs, particularly in patients with pre-existing psychiatric illness [REF]. However high-quality data directly comparing incidence of neuropsychiatric side effects between third agents in non-trial populations are lacking and definitions of side effects between studies are heterogenous. The summary of product characteristics for raltegravir states that raltegravir should be used with caution in individuals with a pre-existing history of psychiatric illness [REF]. We recommend caution when using all INSTIs in individuals with a history of psychiatric illness including depression. However, given that INSTIs have outperformed other classes of ARV agents in clinical trials from an efficacy perspective, and are the recommended therapy

Commented [WA333]: Cuzin L, Pugliese P, Katlama C et al.; Dat'AIDS Study Group. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. J Antimicrob Chemother 2019; 74: 754–760.

Commented [WA334]: Isentress 600 mg film-coated tablets - Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/8436/smpc

for most individuals living with HIV, at this time we do not recommend avoidance of this class. Rather, we recommend caution and close monitoring for neuropsychiatric side effects in those individuals most at risk.

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8.6 Adolescents

The WHO definition of adolescents includes all young people 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 (PaHIV) and behaviourally acquired HIV (BaHIV).

For young people 18 to 24 years of age with BaHIV, the management of their HIV disease and associated considerations should be in accordance with BHIVA guidance for adults. The management of adolescents <16 years of age within paediatric care should be in accordance with Children's HIV Association (CHIVA) guidelines [2] and the Paediatric European Network for Treatment of AIDS (PENTA) treatment guidelines [3], from 2021 incorporated into the EACS guidelines within the paediatric section [4]. There are no randomised controlled trial data on long-term complications of PaHIV and ART exposure during physical development, although observational cohort data are becoming increasingly available and the following recommendations are based on a pragmatic approach and good clinical practice. As for all people living with HIV, any newly

diagnosed adolescent or young person should be carefully counselled and offered ART as soon as possible, ideally as close to the time of diagnosis as appropriate.

8.6.1 Management of HIV, ART and sexual and reproductive health specifically for young adults and adolescents living with HIV

For this specific population, ART should be prescribed in accordance with BHIVA guidance for adults and directed by HIV genotype, anticipated drug side effects and any co-infection and comorbidity. Where alternatives exist, drugs with known association with adverse bone health should be avoided until peak bone mass accrual is achieved, typically at 25 years of age [4].

Recommendation

- We recommend avoiding tenofovir-DF in adolescents and young adults under the age of 25 years, prior to peak bone mass accrual (Grade 2B).

8.6.2 Youth-focused HIV and sexual and reproductive health services

Young adults and adolescents represent a uniquely vulnerable group with poorer 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 healthcare services and primary care and often lack of social support. As such, any service providing care for young adults and adolescents living with HIV must offer appropriate youth-friendly services, with an open-door policy, non-judgemental care provision, opening hours consistent with educational commitments and access to peer support and mental health and reproductive and sexual health services [5]. For young women on boosted PI or efavirenz-based regimens, contraceptive choices will need to be adapted accordingly based on drug–drug interactions [6]; this is particularly relevant to this group as over-the-counter post-coital contraception is now available and may be impacted by drug–drug interactions with ART.

8.6.3 UK Epidemiology for young adults and adolescents living with HIV

Public Health England (PHE) surveillance data have revealed that 10% (315/3165) of all new HIV diagnoses in 2019 were in young people aged 15–24 years, which is a 50% reduction from 2015 [7]. Overall, 231/315 (73%) were male, and the median CD4 count was 423 cells/mm^3 at diagnosis with one-third presenting with a CD4 count <350 cells/mm^3. An additional 80 young adults and adolescents presented for care having previously been diagnosed abroad. Routes of transmission were sex between men (*n*=222), heterosexual contact (*n*=85), perinatal infection (*n*=34), intravenous drug use (*n*=7) and unknown/other (*n*=47). In total

2313 young people aged 15–24 years were accessing HIV care during 2019, representing 2.4% (2313/98,552) of people seen for HIV care in the UK [7]. Of those accessing care, 97% were receiving ART and five young people died.

With ART, the significant fall in HIV-associated morbidity and mortality for children with PaHIV has resulted in increasing numbers entering adolescence and transitioning towards adult services [8-10]. Over 95% of children diagnosed in the UK and reported to the Integrated Screening Outcomes Surveillance Service (ISOSS) were followed prospectively in the Collaborative HIV Paediatric Study [REF]. Data to the end of March 2021 show that 1381/2212 (62%) young people ever reported to CHIPS have now transitioned from paediatric to adult HIV care services, with an average of 100 young people transferring each year over the last 5 years at a median age of 18 years [11]. From January 2022, CHIPS reporting has been replaced by quarterly reporting to the Children's HIV and AIDS Reporting System (CHARS) within ISOSS (https://www.ucl.ac.uk/chars/).

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8.6.4 Transition of clinical care from paediatric to adult services: a process for young adults and adolescents 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 2004 to set standards for the healthcare of young people [12]. Subsequently multiple bodies including NICE and the Royal College of Paediatrics and Child Health have produced a wealth of resources to guide the development of transitional care services [13,14]. Transition is defined as 'a planned, purposeful, process resulting in the point of transfer to adult services'. Several different transition models have been described; the key to a successful transition is communication, forward planning and maintaining a young person-centred approach [15]. HIV-specific transitional care guidance is available through CHIVA and included within the CHIVA Standards [16]. Evidence suggests that a well-managed transition process can have a positive impact on health and wellbeing as young people enter adult services [17,18].

8.6.5 Cognitive and mental health impact of HIV in young adults and adolescents with PaHIV

Recommendation

- Optimising virological control with further investigation and referral to expert HIV neurology clinics for symptomatic individuals is recommended (GPP).

The cognitive impact of living with PaHIV throughout the period of brain development is highly variable with a small proportion having significant learning disabilities and/or hypertonic diplegia, the legacy of infantile

HIV encephalopathy, impacting on independent living. However a larger proportion present with poorer school performance and working memory and executive functioning difficulties, compared to the age-matched general population, although these issues may not be entirely HIV related as some studies suggest a similar pattern in their HIV-exposed uninfected siblings [19-21]. Data suggest that more than two-thirds of treatment-naïve young adults and adolescents with PaHIV meet criteria for a diagnosis of HIV-associated cognitive disorders, with the most common deficits being in memory and fine motor skills [22]. Services need to take into account the potential impact of learning impairment on the ability of young people to negotiate healthcare services including attendance, adherence to ART and quality of life including mental health.

Mental health diagnoses are rising in youth populations and whereas rates of anxiety, depression and substance use in PaHIV and BaHIV appear broadly similar to rates in HIV-exposed uninfected populations, there is a consistent association between mental health diagnoses and poor adherence to ART [23-27]. Emerging data suggest that rates of psychosis are significantly higher in young adults and adolescents with PaHIV than the age-matched general population, although this may in part be driven by traditional risk factors of adverse childhood experiences, migration, ethnicity and poverty [28]. Addressing mental health issues through integrated HIV and mental health services is necessary to optimise quality of life and ART adherence.

8.6.6 ART

8.6.6.1 Adherence

Recommendation

- We suggest that ideally ART should be started with a once-daily regimen with a low pill burden and a high-genetic barrier to resistance based on a second-generation INSTI plus two NRTIs (GPP).

Poorer adherence to ART is reported with increasing age in childhood, as well as in young people with BaHIV, when compared to older adults [8-10]. PHE data for 2019 demonstrate reduced rates of viral suppression (<200 copies/mL) in those aged 15–24 years versus overall rates of viral suppression for those on ART (91% *vs* 97%) and even lower rates for those with PaHIV (89%) [29]. For young people with PaHIV, poor adherence in paediatric care predicts new AIDS diagnoses and mortality following transition to adult care [30-32]. Young adults and adolescents therefore require additional multi-agency adherence support and consideration of novel therapeutic approaches such as long-acting injectable ART [32,33]. There are no specific data to demonstrate better virological suppression with different ART regimens in young adults and adolescents.

Second-generation INSTI-based regimens are the recommended first-line therapy for younger adolescents in the 2021 EACS paediatric guidelines [3].

8.6.6.2 Resistance

Within the UK paediatric cohort, while half of the adolescents with PaHIV are triple-class experienced, rates of triple class resistance are relatively low, ranging from 6–12% [7,9,30]. Decisions regarding the optimal regimen for young adults and adolescents require an individualised approach considering archived resistance, predicted adherence, substance use and mental health.

8.6.6.3 Long-term outcomes for young adults and adolescents with PaHIV

Despite advances in ART, mortality for young adults and adolescents with PaHIV is more than 10-fold higher than the age-matched UK population [9,30,34]. Almost 1 in 10 young people experienced a new AIDS diagnosis and/or death within a median of 3 years post-transition to adult care [30]. Almost all deaths were due to HIV and associated with prolonged poor adherence to ART but not due to multidrug-resistant untreatable virus. Emerging data suggest a 10-fold higher risk of malignancy when compared to age-matched population data, driven by lymphomas [34,35]. In addition to addressing traditional risk factors, including by optimising human papillomavirus and hepatitis B virus vaccination, clinical vigilance for early diagnosis is recommended.

Bone health is adversely affected both in young adults and adolescents with BaHIV and in those with PaHIV, with growth stunting and delayed puberty also affecting the latter group [36,37]. In addition to addressing additional risk factors we recommend, where alternatives exist, avoidance of drugs with known association with adverse bone health until peak bone mass accrual is achieved (see 8.6.1 above) [4]. FRAX scores are only validated from 40 years of age so dual-energy X-ray absorptiometry (DEXA) scanning should be considered for young adults and adolescents with additional risk factors such as prolonged viraemia, reduced mobility, abnormal BMI, growth stunting and recreational/prescription steroid use with referral to dietetic/endocrinology services where appropriate.

8.6.6.4 Clinical monitoring for young adults and adolescents

Recommendations

- We suggest regular rigorous monitoring for hepatic malignancy for adolescents and young adults living with HIV and co-infected with hepatitis B and C (Grade 1C).
- We suggest a high index of suspicion to exclude cervical, anal and vulval intraepithelial neoplasia and lymphoma (Grade 1C).

- We suggest reviewing bone health including DEXA scanning where clinically indicated (Grade 1C).
- We suggest increasing viral load monitoring for pregnant women with PaHIV. Increasing numbers of young adults and adolescents are having children of their own and, although HIV transmission rates in infants are reassuringly low, women with PaHIV are more likely to have detectable viraemia at the time of the birth than women with BaHIV [38] (Grade 1C).
- We suggest early specialist referral for those struggling to conceive irrespective of age due to preliminary data suggesting a possible reduction in fertility [39] (Grade 1C).

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8.7 Bone disease

8.7.1 What to start

Recommendation

- We recommend against the use of tenofovir-DF in individuals with osteoporosis, a history of fragility fracture or a FRAX score of >10% (major osteoporotic fracture) (Grade 1B).

Rationale

Several randomised controlled clinical trials comparing tenofovir-DF-containing and tenofovir-DF-sparing regimens in ART-naïve individuals have reported greater reductions in BMD in the tenofovir-DF arms. A study comparing abacavir/lamivudine versus tenofovir-DF/emtricitabine (each with efavirenz) reported greater reductions in BMD at the lumbar spine (–1.6% *vs* –2.4%) and the hip (–1.9% *vs* –3.6%), and greater proportions of participants with >6% BMD reductions (3–6% *vs* 13–15%) in the tenofovir-DF-containing arm at week 48 [11]. Another study comparing abacavir/lamivudine versus tenofovir-DF/emtricitabine (each with efavirenz or atazanavir/ritonavir) reported BMD reductions of –1.3% versus –3.3% at the lumbar spine and

–2.6% and –4.0% at the hip at week 96 [12]. Greater reductions in BMD have also been reported in a study comparing tenofovir-AF versus tenofovir-DF (each with emtricitabine/elvitegravir/cobicistat): –0.9% versus –3.0% at the lumbar spine and –0.8% versus –3.4% at the hip at 144 weeks [13]. A further study of tenofovir-AF versus tenofovir-DF (each with emtricitabine/darunavir/cobicistat) reported greater BMD reductions in the tenofovir-DF arm at the lumbar spine (+0.21% *vs* –2.73%) and hip (–0.68 *vs* –2.38%) [14]. A meta-analysis of studies in ART-naïve individuals found that the proportion of individuals on tenofovir-AF-containing versus tenofovir-DF-containing regimens who experienced greater than 3% reduction in BMD was 26.7% versus 47.0% at the lumbar spine, and 16.3% versus 50.1% at the hip [15]. No differences in the incidence of fractures have been reported in these studies of relatively short duration, and no differences in BMD at the lumbar spine or hip have been reported in a trial that compared abacavir/lamivudine versus tenofovir-AF/emtricitabine (each with bictegravir) up to 144 weeks [16]. Altogether, these data support the use of tenofovir-AF/emtricitabine and abacavir/lamivudine in preference to tenofovir-DF/emtricitabine as part of initial regimens for people living with HIV who have osteoporosis, severe osteopenia and/or high fracture risk.

Clinical trial data on the effects of PIs on BMD in treatment-naïve individuals are relatively sparse. A study comparing BMD at the spine and hip in individuals randomly assigned to efavirenz or atazanavir/ritonavir (each with abacavir/lamivudine or tenofovir-DF/emtricitabine) reported significantly greater reductions in BMD at the spine (–0.8% *vs* –2.0% with abacavir/lamivudine; –2.5% *vs* –4.4% with tenofovir-DF/emtricitabine), but not at the hip (–2.5% *vs* –2.7% with abacavir/lamivudine; –3.8% *vs* –4.4% with tenofovir-DF/emtricitabine), with atazanavir/ritonavir [12]. When analysed together with two other ACTG studies, randomisation to ritonavir-boosted PIs resulted in a 0.8% greater reduction in total BMD [17]. Greater reductions in BMD at 96 weeks were reported for PIs (atazanavir/ritonavir or darunavir/ritonavir) versus raltegravir (each with tenofovir-DF/emtricitabine): –3.8% versus 1.8% at the lumbar spine and –3.7% versus –2.4% at the hip [18]. It is possible that increased tenofovir concentrations, as occur when tenofovir-DF is co-administered with boosted PIs, may account for these differential effects on BMD. There are no data for boosted PIs versus unboosted third agents in regimens containing tenofovir-AF/emtricitabine, and insufficient data to make firm recommendations regarding the third agent in terms of their effect on BMD.

8.7.2 Switching treatment

Recommendation

- We recommend against continued use of tenofovir-DF in individuals who are diagnosed with osteoporosis, have sustained a fragility fracture or have a FRAX score of >10% (major osteoporotic fracture) (Grade 1B).

Rationale

In randomised controlled clinical trials of individuals who were virologically suppressed on ART including older people with HIV, switching from a tenofovir-DF-containing to a tenofovir-AF-containing regimen resulted in improvements in BMD at the lumbar spine (1.5–2.2%) and the hip (1.3–1.9%) [19-22]. Similar results have been obtained with switches to abacavir [23], raltegravir [24], dolutegravir/rilpivirine [25] or darunavir/ritonavir monotherapy [26]. No changes in BMD at the lumbar spine and hip were observed in individuals switching from abacavir/lamivudine to tenofovir-AF/emtricitabine [27]. In cohort studies, tenofovir-DF has been associated with low BMD and bone loss [3,28-31], and a modest (8–13%) increased incidence of fracture in some studies [8,9] but not in others [10].

Although cohort studies have also identified an association between exposure to PIs and reductions in BMD [28,31] and an improvement in spine BMD in individuals who discontinued PIs [32], there are no data from ART switch studies to suggest that PI discontinuation improves BMD, and no consistent association between PI use and fracture has been observed [8-10]. An association between PIs and avascular necrosis was reported in a meta-analysis of four case–control studies [33] but not confirmed in the EuroSIDA study [9].

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8.8 Later life

8.8.1 Introduction

People with HIV are not only living into older age but older people are also acquiring HIV as they maintain sexually active lifestyles. The proportion of people living with HIV in the UK aged ≥50 years has more than doubled in the last decade. In 2019, 43% of adults (aged >15 years) seen for HIV care in the UK were aged ≥50 years, compared with 21% in 2010 [1]. Older people living with HIV are more likely to experience comorbidities and be receiving non-ARV medication. In addition, increased age may be associated with a higher prevalence of mental health issues, social isolation and financial challenges; HIV-treating clinicians should be mindful of these factors and familiar with appropriate sources of support.

8.8.2 When to start ART

Recommendation

- We recommend that standard criteria are used to determine when to commence ART in older people with HIV (Grade 1C).

Rationale

The following factors should be specifically considered.

8.8.2.1 Rate of CD4 cell count decline

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

Commented [CNS336]: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group, Sabin CA, Smith CJ, d'Arminio Monforte A, et al Response to combination antiretroviral therapy: variation by age. AIDS. 2008 Jul 31;22(12):1463-73.

8.8.2.2 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, which is an important factor to consider when counselling older individuals about starting ART.

8.8.2.3 CD4 cell count recovery on commencing ART

CD4 cell count 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 count [5,7,8]. Some studies suggest that this is a short-term phenomenon attenuated with longer duration of ART [9] and others suggest that CD4 cell count recovery and virological suppression are not affected by age [10,11].

8.8.2.4 Non-infectious comorbidities

Individuals living with HIV may experience a higher rate of age-related conditions than the general population. 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 comorbidities, including fat changes, atherosclerosis and sarcopenia [12].

8.8.3 What to start

Recommendation

- We recommend that standard ART regimens are commenced in older people with HIV (Grade 1C).

Rationale

The factors below should be specifically considered when commencing therapy in older people living with HIV.

8.8.3.1 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 people with HIV compared to matched control populations [13]. The possibility of end-organ disease should be considered when tailoring ART for older individuals.

8.8.3.2 Concomitant medication

The use of concomitant medication, both over-the-counter preparations and prescription medication, is highly prevalent in older people living with HIV [14]. Consideration of drug–drug interactions with concomitant medications is required when commencing ART in older people with HIV.

8.8.3.3 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 ARV drugs, effects on hepatic metabolism and elimination may be relevant [15]. 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-PIs has been reported to increase with age [16], with these effects not reported with other classes such as the INSTIs 17]. Although theoretically this could lead to increased toxicity in older people living with HIV, 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 compared to younger people living with HIV, which was thought to be due to reduced renal clearance [18]. Again, there is a theoretical risk of increased toxicity as a result of higher drug exposure.

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8.9 Transgender people

Recommendations

- Transgender people living with HIV may be impacted disproportionately by some of the key considerations around ART choice (e.g. drug–drug interactions, mental health concerns, stigma, CVD and low BMD); holistic assessment is advised when selecting optimal ART (GPP).
- We recommend that clinics collect accurate data on gender identity so that data on the outcomes and experiences of transgender people living with HIV can be used to better tailor services (GPP).
- We recommend individualised interpretation of gender-influenced laboratory and other assessments that may impact ART choice (GPP).

Rationale

Transgender is defined by the Office for National Statistics as an umbrella term for people whose gender identity is different from the sex assigned at birth [REF]. Of note the Equality Act 2010 includes gender reassignment (defined as proposing to undergo, undergoing or has undergone a process, or part of a process, for the purpose of reassigning the person's sex by changing physiological or other attributes of sex) as a protected characteristic [REF].

It is important for HIV care providers to gain understanding and support the specific care needs of transgender people. Transgender populations are at higher risk of HIV acquisition [REF] and are impacted disproportionately by factors that may impact adherence and drug toxicity, and therefore ART choice.

There are no robust data on the number of people in the UK who identify as transgender though the Government offers a 'tentative estimate' of 200,000 to 500,000 individuals [REF]. Government data demonstrate lower quality of life scores among people in the lesbian, gay, bisexual and transgender (LGBT) community in general, and scores are particularly low for those who identify as transgender [REF].

Importantly, HIV prevalence among transgender and gender-diverse people in England has been reported to be relatively low compared with international estimates [REF]. However, estimates of undiagnosed HIV prevalence among transgender populations are high compared with cisgender populations and structural barriers may prevent transgender people from HIV testing [REF].

Individual assessment of current and future health needs is of the utmost importance for transgender people. For example, understanding pregnancy plans, need for cervical screening and access to interventions such as human papilloma virus vaccination can help ensure transgender people receive optimal care.

Commented [WLJ(ANWLN337]: Office for National Statistics. What is the difference between sex and gender? Available at: https://www.ons.gov.uk/economy/environmentalaccounts/articles/whatisthedifferencebetweensexandgender/2019-02-21#:~:text=Transgender,-Transgender%20or%20trans&text=%E2%80%9CA%20person%20has%20the%20protected,or%20other%20attributes%20of%20sex.%E2%80%9D **(accessed April 2022).**

Commented [WLJ(ANWLN338]: Equality Act 2010. Available at: https://www.legislation.gov.uk/ukpga/2010/15/contents (accessed April 2022)

Commented [MB339]: Becasen JS, Denard CL, Mullins MM, et al. Estimating the Prevalence of HIV and Sexual Behaviors Among the US Transgender Population: A Systematic Review and Meta-Analysis, 2006-2017. Am J Public Health 2018 Nov 29:e1-e8.

Commented [WLJ(ANWLN340]: Accessed ato https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/721642/GEO-LGBT-factsheet.pdf 12 April 2022

Commented [WLJ(ANWLN341]: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/722314/GEO-LGBT-Survey-Report.pdf 12 April 2022

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Commented [MB343]: Baral SD, Poteat T, Stromdahl S, Wirtz AL, Guadamuz TE, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13** (3): 214–222

8.9.1 Accessing care

In England, between 2017 and 2020, 4–6% of individuals newly diagnosed with HIV were transgender or gender diverse people of whom more than 96% were initiated on ART.

Transgender people may experience numerous barriers to successful engagement with HIV care services [REF].

A Stonewall survey revealed that 41% of transgender men and women had experienced a hate crime or incident because of their gender identity [REF]. They also reported that 25% of transgender people had experienced homelessness at some point in their lives. A Government led national LGBT survey found similar results, with 67% of transgender respondents saying they had avoided being open about their gender identity for fear of a negative reaction from others [REF].

Transgender people may avoid the healthcare system due to stigma and past negative experiences (e.g. being called the wrong name or pronoun, being verbally harassed, asked invasive questions about being transgender, or having to educate their providers about transgender people) [REFS].

We recommend ensuring that registration forms and electronic medical records are inclusive of transgender and gender non-binary identities (e.g. record both gender and sex assigned at birth) (GPP):

- All people should be asked for their chosen name and pronouns, and these should be used consistently when speaking to or about the person, regardless of legal name.
- Training for staff and brochures, and other materials that meet the specific needs of transgender people living with HIV, should be available.

8.9.2 Peer support

Peer navigation has been found to improve the likelihood of durable viral suppression among key populations, including among transgender women [REF]. Research with youth and adults suggests that having visible transgender staff in the clinical environment also facilitates engagement in care.

8.9.3 ART outcomes

For the reasons outlined above, transgender people may be particularly affected by adherence challenges.

Some studies have shown that transgender women living with HIV are less likely than cisgender men to receive ART, be adherent to ART, and achieve viral suppression [REFS].

Commented [MB344]: -Poteat T, Hanna DB, Rebeiro PF, et al. Characterizing the HIV care continuum among transgender women and cisgender women and men in clinical care: a retrospective time-series analysis. *Clinical Infectious Diseases*. 2019.
-Kalichman SC, Hernandez D, Finneran S, Price D, Driver R. Transgender women and HIV-related health disparities: falling off the HIV treatment cascade. *Sex Health*. 2017;14(5):469-476.

Commented [WLJ(ANWLN345]: Government Equalities Office. Trans people in the UK. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/721642/GEO-LGBT-factsheet.pdf

Commented [WLJ(ANWLN346]: As above https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/721642/GEO-LGBT-factsheet.pdf

Commented [WLJ(ANWLN347]: Poteat T, German D, Kerrigan D. Managing uncertainty: a grounded theory of stigma in transgender health care encounters. *Soc Sci Med*. 2013;84:22-29.

Commented [WLJ(ANWLN348]: Cunningham WE, Weiss RE, Nakazono T, et al. Effectiveness of a peer navigation intervention to sustain viral suppression among HIV-positive men and transgender women released from jail: the LINK LA randomized clinical trial. *JAMA Intern Med*. 2018;178(4):542-553.

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AND Poteat as above:
Poteat T, German D, Kerrigan D. Managing uncertainty: a grounded theory of stigma in transgender health care encounters. *Soc Sci Med*. 2013;84:22-29.

8.9.4 Drug–drug interactions

Gender-affirming hormone therapy (GAHT) may have drug–drug interactions with some ARVs. The University of Liverpool website has a specific prescribing resource on interactions with GAHT [REF].

GAHT may be a greater priority than HIV treatment [REF] and fear of drug–drug interactions between ART and GAHT is common among transgender people [REF]. Ensuring that people taking GAHT, or planning to, are provided with clear, accurate information about any potential interactions with ART may help address these concerns.

8.9.5 CVD risk

Elevated CVD risk in transgender individuals can be due to both traditional risk factors and to hormone use. Rates of tobacco use are higher among transgender people [REF], and transgender women have a higher risk of venous thromboembolism and ischaemic stroke, associated with the use of oestrogens [REF]. Oestrogens may cause an increase in triglycerides and high-density lipoprotein (HDL) levels and a decrease in low-density lipoprotein (LDL) levels, whereas exogenous testosterone was reported to increase levels of LDL and decrease levels of HDL [REF].

Specific guidance for estimating CVD risk for transgender people is lacking and evidence is required. Clinicians should take CVD risk into consideration when selecting ART regimens and GAHT regimens.

Clinicians are advised to use the risk calculator for the sex at birth, affirmed gender, or an average of the two, considering the age at which the individual started using hormones, and the amount of time that a patient has been on GAHT [REF].

8.9.6 Bone health

Bone metabolism is influenced by sex hormones. Current recommendations for osteoporosis screening are based on age and sex and have not been studied in transgender populations, which include people who have used hormone therapy and/or undergone surgical gender affirmation.

Studies investigating BMD changes in transgender women have shown inconsistent results, with the use of oestrogens being associated with both increases and decreases in BMD [REFs]. The risk of osteoporosis increases after gonadectomy for both transgender men and transgender women, especially if GAHT regimens are stopped. Consequently, early DEXA screening in this setting should be considered.

Commented [WLJ(ANWLN350]: University of Liverpool. HIV Drug Interactions. https://www.hiv-druginteractions.org/prescribing_resources accessed April 2022

Commented [WLJ(ANWLN351]: Sevelius JM, Patouhas E, Keatley JG, Johnson MO. Barriers and facilitators to engagement and retention in care among transgender women living with human immunodeficiency virus. *Ann Behav Med*. 2014;47(1):5-16.

Commented [WLJ(ANWLN352]: Sevelius JM, Patouhas E, Keatley JG, Johnson MO. Barriers and facilitators to engagement and retention in care among transgender women living with human immunodeficiency virus. *Ann Behav Med*. 2014;47(1):5-16.

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Commented [MB356]: University of California, San Francisco. Transgender care. Cardiovascular Disease. https://transcare.ucsf.edu/guidelines/cardiovascular

Commented [WLJ(ANWLN357]: Fighera T.M., Ziegelmann P.K., Rasia da Silva T., Spritzer P.M. Bone mass effects of cross-sex hormone therapy in transgender people: updated systematic review and meta-analysis. *J Endocr Soc.* 2019;3(5):943–964.

When using the FRAX score, which requires a sex designation, expert consensus is that assigned birth sex should be used, because transgender people who initiate hormones in early adulthood have generally already achieved peak bone mass [REF].

Commented [WLJ(ANWLN358]: University of California, San Francisco. Transgender care. Bone health and osteoporosis. https://transcare.ucsf.edu/guidelines/bone-health-and-osteoporosis

8.9.7 Renal function

GAHT may affect eGFR that relies on serum creatinine due to changes in muscle mass. Creatinine-based eGFR calculations may therefore overestimate eGFR in transgender women on GAHT or underestimate eGFR in transgender men on GHAT. Cystatin C-based or isotopic eGFR calculations may be preferred, if available, for patients with marginal renal function.

There are conflicting data regarding use of identified gender versus sex at birth in eGFR calculators with some studies suggesting sex at birth yields more accurate results, other studies showing identified gender to be more accurate, and one study suggesting identified gender should be used where an individual as been on GAHT for at least 6 months [REF]. In the absence of definitive research, we advise individualised assessment, careful monitoring of trends and urine markers of renal impairment, and conservative interpretation of results that might impact ART choice.

Commented [WLJ(ANWLN359]: Jue JS, Mikhail D, González J, Alameddine M. Assessment of Renal Function in Transgender Patients With Kidney Disease. Can J Kidney Health Dis. 2021 Jun 4;8:20543581211020168. doi: 10.1177/20543581211020168. PMID: 34158966; PMCID: PMC8182218.

8.10 Chronic liver disease

Chronic liver disease remains relatively common in people living with HIV. While co-infection with hepatitis B and C and related liver fibrosis remain challenges, progress in therapy of viral hepatitis means that alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) are increasingly important.

For patients being considered for hepatitis C virus therapy, drug–drug interactions need to be considered and there are some contraindicated combinations of hepatitis C and HIV therapy (particularly with PI-based hepatitis C therapy). Clinicians should consult specialist guidelines and refer to the dedicated pages of the Liverpool website [REF].

Commented [CNS360]: University of Liverpool. HEP Drug Interactions. www.hep-druginteractions.org

Alterations to drug choice and dosing of ART regimens may be required in the setting of liver fibrosis. Dose adjustments are not usually required in those with mild fibrosis alone, but in the setting of cirrhosis, specific guidelines [REF] should be consulted. Evidence is limited for many settings and TDM may be helpful where there is clinical uncertainty.

Commented [CNS361]: EACS guidelines https://www.eacsociety.org/media/2019_guidelines-10.0_final.pdf

In the setting of NAFLD, both an individual's liver health and their overall CVD risk profile and weight need to be considered when selecting ART. While some agents (e.g. INSTIs) are associated with more favourable lipid

profiles and may be preferred in the setting of advanced liver disease, they may also be associated with weight gain that could impact liver health.

9 Acknowledgements

To be added after consultation.

10 List of appendices

The appendices can be found on the BHIVA website (www.bhiva.org/HIV-1-treatment-guidelines)

Appendix 1 Summary of the modified GRADE system

Appendix 2 PICO questions and search strategies

Appendix 3 Grade tables