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SUPPLEMENT ARTICLE

British HIV Association guidelines for the management of HIV-2 2021

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1 | INTRODUCTION

Human immunodeficiency virus (HIV) is classified into two main types: HIV-1, which is closely related to a simian immunodeficiency virus (SIV) in chimpanzees, and HIV-2, which is closely related to an SIV in sooty mangabeys (SIVsmm) [1]. HIV-2 has a number of subtypes but only groups A and B have become epidemic [2]. HIV-2 is a much less common HIV type than HIV-1; the exact prevalence is unknown, but an estimate has been made of 1–2 million people living with HIV-2 worldwide, including those with dual HIV-1 and HIV-2 infection [2]. There are few current reliable prevalence estimates and the widely used rapid testing methods for HIV do not distinguish between HIV-1 and HIV-2 [3]. Although endemic in West Africa, the distribution of HIV-2 is limited and low prevalence in most settings, which means that understanding and experience of HIV-2, relative to HIV-1, among clinicians are often lacking. In addition, the majority of cohort and treatment studies quoted below, relate only to group A, adding to clinical uncertainty. Since HIV-2 was first recognised, evidence has accumulated regarding pathogenicity and prognosis. Although HIV-2 was initially considered non-pathogenic, it is now known that most untreated individuals with HIV-2 will experience disease progression, albeit at a slower rate compared to those with HIV-1 [4]. Diagnosis, monitoring and management of HIV-2 remain challenging. Antiretroviral drugs are mostly developed for

activity against HIV-1 group M, therefore many are inactive against HIV-2 and there are limited *in vitro* data for those drugs that may be used. To date, there have been no published randomised controlled trials of antiretroviral therapy (ART) for HIV-2 and our understanding is based on cohort studies and observational data.

There are important differences in natural history between HIV-1 and HIV-2. HIV-2 carries a lower risk of horizontal and vertical transmission related to much lower plasma viral load, which is often undetectable without ART [1]. There is a slower CD4 T-cell decline but some AIDS-defining illnesses may develop at higher CD4 counts [4]. The disease trajectory of HIV-1 and HIV-2 is almost identical but progresses at approximately half the rate in HIV-2 so that a prolonged asymptomatic phase is more common. However, disease progression is likely eventually to occur in the majority of individuals with HIV-2 in the absence of ART [4]. Clinical disease due to HIV-2 is indistinguishable from that due to HIV-1. Resistance mutations in protease and reverse transcriptase can develop commonly in HIV-2 as the resistance barrier is lower and their effect on treatment efficacy is less well clinically characterised than in HIV-1 [5].

HIV-2 infection does not protect against HIV-1 infection and dual infection may occur. One study has shown that HIV-2 prior to acquisition of HIV-1 in dual infection delays clinical progression, compared to HIV-1 mono-infection [6].

1.1 | Origin of HIV-2

HIV-2 was initially isolated in 1986 [7] and the first sequence published in 1987 [8]. It had been observed that some individuals had an unusual serological profile, more closely related to simian lentiviruses than HIV-1; it was subsequently shown that the animal origin of HIV-2 is SIVsmm [9]. Sooty mangabeys are native to the forests of coastal West Africa where a high prevalence of SIVsmm has been demonstrated, are hunted for food and are often kept in captivity as pets. It has been estimated that species jump into humans occurred between 1905 and 1942 for HIV-2 group A and between 1914 and 1945 for group B (which has been less extensively studied) [1,10,11].

Nine distinct lineages of HIV-2 have been identified, termed groups A to I. Only HIV-2 groups A and B are endemic; all other HIV-2 groups have been identified in only one or two individuals. HIV-2 group A is more common and has a distinct geographical origin from group B. There do not seem to be clinical differences between groups A and B, but data are lacking. Each of the nine HIV-2 groups is thought to represent a single cross-species viral transmission. The non-endemic groups are considered to be 'dead-end' infections representing continuing transmissions of SIVsmm to humans. In contrast to HIV-1, recombination events are rare; only one circulating recombinant and one unique recombinant form have been described.

1.2 | Epidemiology of HIV-2

HIV-2 is mainly restricted to West Africa. The highest prevalence has been observed in Guinea-Bissau, The Gambia, Senegal, Cape-Verde, Côte d'Ivoire and Sierra Leone, which all reported >1% general population prevalence in the 1980s. Guinea-Bissau had the highest reported prevalence at 8% in adults and up to 20% in individuals aged over 40 years in 1987 [12]. HIV-2 is also found in Ghana, Burkina Faso and Mali and has dispersed to Angola, Mozambique, Brazil, India and Europe. A significant increase in the number of new HIV-2 infections in Guinea-Bissau in the mid-1960s is attributable to the war of independence (1963–1974) and is linked to the expansion and dissemination of HIV-2 to Portugal and its former colonies [1]. HIV-2 is increasingly recognised in parts of India, especially those with previous connections to Portugal such as Goa and Maharashtra states. Relatively high prevalence in some areas is thought to be driving a significant prevalence of dual HIV-1 and HIV-2 infections in India [13]. Portugal and France have the highest number of people living with HIV-2 in Europe with approximately 2000 and 1000 people respectively [14]. HIV-2 has been reported in a number of other countries, including Spain, Germany, the UK and the USA [15-18].

Studies from Guinea-Bissau, The Gambia and Senegal have shown a recent rapid decrease in the prevalence of HIV-2 resulting in speculation that the infection may become extinct by the middle of the 21st century [19-21]. The decreasing prevalence of HIV-2 may be due to its lower transmission risk, changes in risk behaviours, reduced risk of healthcare-associated infections and/or competition with HIV-1 [22,23]. Notable in these studies is the finding that HIV-2 prevalence has declined more among women than men, while older women seem to maintain a higher risk of acquiring infection than older men [22,24].

1.3 | Guideline development process

Full details of the guideline development process, including conflict of interest policy, are outlined in the British HIV Association (BHIVA) guideline development manual which was last updated in 2020 (see https://www.bhiva.org/file/jgCacHqmuxZFL/GuidelineDevelopmentManual.pdf). The scope, purpose and guideline topics were agreed by the writing group. Questions concerning each guideline topic were

drafted and an independent systematic literature review carried out. For the current guidelines, Medline, Embase and the Cochrane Library were searched for English language publications between January 2016 and September 2019 using the search terms HIV-2 or HIV2; animal studies were excluded. Abstracts from selected conferences (BHIVA, Conference on Retroviruses and Opportunistic Infections, IAS Conference on HIV Science, International AIDS Conference and HIV Drug Therapy Glasgow) were also searched for the same period.

For each topic, evidence was identified and evaluated by writing group members with expertise in the field. Using the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (see Appendix 1), writing group members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. Good practice points (GPPs) are recommendations based on the clinical judgment and experience of the working group. GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence, but where the aspect of care is regarded as such sound clinical practice that healthcare professionals are unlikely to question it and where the alternative recommendation is deemed unacceptable.

Before final approval by the writing group, the guidelines were published online for public consultation and external peer reviews were commissioned.

A full review of these guidelines is due in September 2026, with interim updates only if recommendations need updating in line with new data.

2 | SUMMARY OF RECOMMENDATIONS

3 Supporting people living with HIV-2

- We recommend that the same principles for involving people with HIV-1 in their care are followed for those with HIV-2. (GPP)
- In providing treatment and peer support, particular care must be taken to give accurate information, given the differences between HIV-1 and HIV-2. (GPP)
- Adherence support is particularly important, owing to limited treatment options. (GPP)

4 Clinical standards

- We suggest that the BHIVA clinical standards [25] are likely to be appropriate for people living with HIV-2. (Grade 2D)

5 Diagnosis of HIV-2 infection

5.1 Laboratory diagnosis of chronic HIV-2 infection

- We recommend that an initial diagnosis of chronic HIV-2 infection should be made using a total of three CE-marked serology tests (i.e. tests conform to EU health and safety requirements) performed in an ISO 15189-accredited laboratory. There must be reactivity in two CE-marked fourth-generation tests for HIV-1 and HIV-2, followed by differentiation of HIV-2 by a third CE-marked antibody-only test. (Grade 1A)
- Clinicians should consider revisiting a previous diagnosis of HIV-1 by repeating HIV-2 serology and molecular tests in individuals with an undetectable HIV-1 viral load in the absence of ART, but a falling CD4 count. This is in order to detect the possibility of missed HIV-1 and HIV-2 dual infection. (GPP)
- Similarly, in those with diagnosed HIV-2 with an undetectable viral load in the absence of ART, clinicians should consider repeating HIV-1 diagnostic tests, if their CD4 count falls. This is to investigate the possibility of HIV-1 superinfection. (GPP)

5.2 Laboratory diagnosis of acute primary HIV-2 infection

- We recommend that investigation for acute or very recent HIV-2 infection should start as for diagnosis of chronic HIV-2 infection. A negative HIV-2 screening result on a blood sample taken within 3 months of the likely exposure should be further investigated at 6 weeks and 3 months, with parallel testing for HIV-2 viral RNA and, if necessary, HIV-2 proviral DNA. (Grade 1A)

5.3 Indeterminate HIV-1 or HIV-2 serology: how to investigate further

- We recommend that *any* HIV-1 or HIV-2 serology that does not fit into a clear pattern of a confirmed laboratory diagnosis is fully investigated for the presence or absence of HIV-2 infection, and that this should be established by PCR for HIV-2 proviral DNA. (Grade 1A)

5.4 Measuring HIV-2 viral load

- People with HIV-2 should have viral load measured at baseline and then repeated at appropriate intervals (see Section 8 Monitoring). (Grade 1A)

5.5 Resistance testing

- Resistance testing should be performed at diagnosis, prior to treatment initiation and at virological failure, if the

HIV-2 viral load meets the threshold of ≥500 copies/mL. (Grade 1C)

6 When to start treatment

- It is essential that the risks and benefits of initiating ART are discussed with all individuals with HIV-2. (GPP)
- We suggest that all people with HIV-2 start ART. (Grade 2C)
- We recommend that people with HIV-2 start ART in the following circumstances:
  - If there is dual HIV-1 and HIV-2 infection; (Grade 1A)
  - When a diagnosis is made during primary HIV-2 infection; (Grade 1C)
  - If there is co-infection with hepatitis B (HBV); (Grade 1C)
  - In pregnancy (see Section 9.1 Pregnant women); (Grade 1C)
  - If there is detectable HIV-2 viraemia; (Grade 1B/C)
  - If the CD4 count is below 500 cells/mm^3; (Grade 1B)
  - In advanced HIV disease, or if there are opportunistic infections; (Grade 1B)
  - If there are symptoms, or an indicator condition for HIV-1 and/or HIV-2, regardless of CD4 count or viral load. (Grade 1C)
- We suggest that additional consideration is given to starting ART if there are significant comorbidities. (Grade 2D)

6.1 Chronic infection

- We suggest that people with HIV-2 start ART. (Grade 2C)

6.2 Individuals with dual HIV-1 and HIV-2 infection

- We recommend that people with dual HIV-1 and HIV-2 infection start ART, with a regimen selected to provide full suppression for both viruses. (Grade 1A)

6.3 Treatment of primary HIV-2 infection

- We recommend that people diagnosed with HIV-2 during primary HIV-2 infection start ART. (Grade 1C)

6.4 Individuals with HBV co-infection

- We recommend that all people with HIV-2 who are co-infected with HBV are treated with fully suppressive ART that provides activity against both viruses. (Grade 1C)

6.5 Individuals with a detectable HIV-2 viraemia

- We recommend that people with HIV-2 start ART if there is detectable HIV-2 viraemia. (Grade 1B)

6.6 Individuals with a CD4 cell count below 500 cells/mm^3

- We recommend ART initiation for all people with HIV-2 with a CD4 cell count below 500 cells/mm^3. (Grade 1C)

6.7 In advanced HIV disease or the presence of opportunistic infections

- We recommend that all people with HIV-2 who have advanced HIV disease or a current or previous opportunistic infection start ART. (Grade 1B)

6.8 In the presence of an indicator condition for HIV

- We recommend that all people with HIV-2 who are symptomatic or have a current or previous indicator condition for HIV start ART. (Grade 1C)

6.9 Comorbidities

- We suggest that additional consideration is given to starting ART if there are significant comorbidities. (Grade 2D)

7 What to start

- It is recommended that people with HIV-2 start ART containing two NRTIs plus one of the following: a second-generation INSTI or a ritonavir-boosted PI (PI/r). (Grade 1C)
- Two-drug regimens currently in use for treatment of HIV-1 are not recommended. (Grade 1D)
- NNRTIs are not recommended in the treatment of HIV-2. (Grade 1C)

7.2 Which NRTI backbone

- We recommend that tenofovir disoproxil (DX) with emtricitabine is the preferred NRTI backbone. (Grade 1C)
- Tenofovir alafenamide (AF) with emtricitabine is a suggested alternative NRTI backbone if there are clinical reasons to prefer it over tenofovir DX. (Grade 2C)
- Abacavir with lamivudine is another suggested alternative NRTI backbone if there are clinical reasons to avoid both tenofovir prodrugs. (Grade 2D)

7.3 Which third agent

- We recommend that therapy-naïve individuals start ART containing dolutegravir or darunavir/r as the preferred third agent. (Grade 1C for both)

- Bictegravir is a suggested alternative INSTI if clinically appropriate. (Grade 2D)
- Cobicistat is an alternative pharmacokinetic enhancer if clinically appropriate. (Grade 2D)
- Raltegravir is a suggested alternative INSTI if clinically appropriate. (Grade 2C)
- Cobicistat-boosted elvitegravir is a suggested alternative INSTI if clinically appropriate. (Grade 2C)
- We suggest that lopinavir/r should be reserved for those who cannot tolerate either darunavir/r or dolutegravir or when there are clinical reasons to avoid the other third agents listed above. (Grade 2C)

8 HIV-1 and HIV-2 co-infection

- Consider the viral load and resistance profiles for both viruses when selecting treatment. (GPP)
- We recommend that, if there is a clinical reason to start treatment before a definitive diagnosis is made, treatment is started as for HIV-2 using twice daily dosing of either dolutegravir or boosted darunavir. (Grade 1D)

9 Monitoring

- In individuals who are not on treatment, CD4 cell counts should be measured at 3- to 6-month intervals depending on the baseline value and rate of decline of CD4 count. (Grade 1B)
- In individuals who are not on treatment, the viral load should be measured at baseline and every 6 months. (Grade 1C)
- Baseline testing for NRTI, PI and INSTI resistance should be performed prior to starting ART; a sample should be retained if resistance testing is not possible. (Grade 1C)
- In those who are taking ART, the CD4 cell count should be measured at 1, 3 and 6 months after starting or changing ART and 3–6 monthly thereafter depending on the nadir CD4 cell count. (Grade 1C)
- If the pre-treatment viral load was detectable, the viral load should be measured at 1, 3 and 6 months after starting or changing ART and then 3–6 monthly. (Grade 1C)
- If the pre-treatment viral load was undetectable, the viral load should be measured at 1 month and then 6 monthly. (Grade 1C)
- The HIV viral load should be repeated in those on ART where the HIV-2 RNA has been maximally suppressed and becomes detectable. (Grade 1D)
- Testing for drug resistance should be performed in those on ART where the HIV-RNA has been maximally suppressed and becomes repeatedly detectable. (Grade 1C)

10 Pregnant women and neonatal post-exposure prophylaxis

10.1 Pregnant women

- We recommend that pregnant women with HIV-2 should initiate ART, if they are not already established on an effective regimen. (Grade 1C)
- We recommend that an effective ART regimen already established at conception should be continued. (Grade 1C)
- We recommend tenofovir DX with emtricitabine as the preferred NRTI backbone. (Grade 1C)
- We recommend darunavir/r as the preferred third agent. (Grade 1C)
- Dolutegravir may be used or continued as a preferred third agent, taking into consideration the possible risks and benefits for the woman. (Grade 1C)
- Case discussion with experts with experience of managing HIV-2 is recommended for all pregnant women. (Grade 1D)
- Women with HIV-2 who wish to conceive should be informed about the possible risks associated with dolutegravir use around the time of conception. (GPP)

10.2 Neonatal post-exposure prophylaxis

- Infants who are defined as being at very low or low risk of vertical transmission should receive zidovudine monotherapy. (Grade 1D)
- We suggest that the duration of zidovudine monotherapy should be 2 weeks and 4 weeks for very low-risk and low-risk infants, respectively, stratified as per the BHIVA HIV-1 pregnancy guidelines. (Grade 2D)
- Infants who are defined as being at high risk of vertical transmission should receive triple therapy with zidovudine/lamivudine/raltegravir. (Grade 1D)

11 Managing treatment failure

- Genotypic resistance testing should be attempted in the event of virological rebound. (Grade 1C)
- Algorithmic resistance mutation analysis should be utilised if resistance is detected. (Grade 1D)
- We suggest that specialist advice is sought from a clinician with experience in managing HIV-2. (Grade 2D)
- Fully active agents should be used to construct a second-line regimen in the case of resistance, though it may be necessary to continue partially active agents in order to maximise overall regimen activity. (Grade 1D)

12 PEP and pre-exposure prophylaxis for sexual exposure to HIV-2

- We suggest that PEP after sexual exposure and pre-exposure prophylaxis (PrEP) used for HIV-1 are likely to be effective against HIV-2. (Grade 2D)

3 | SUPPORTING PEOPLE LIVING WITH HIV-2

Recommendations

- We recommend that the same principles for involving people with HIV-1 in their care are followed for those with HIV-2. (GPP)
- In providing treatment and peer support, particular care must be taken to give accurate information, given the differences between HIV-1 and HIV-2. (GPP)
- Adherence support is particularly important, owing to limited treatment options. (GPP)

Rationale

Although there may be many similarities in the way HIV-1 and HIV-2 are treated and managed, there are also significant differences that need to be clearly understood. In the UK, HIV-1 is by far the more common diagnosis, and almost all of the available patient information is written for people living with HIV-1. As a result, the differences between HIV-1 and HIV-2 may be poorly understood, and so special effort must be made to inform people living with HIV-2 and their partners about these differences, as they affect important aspects of diagnosis, treatment and ongoing management.

Most people living with HIV-2 in the UK either have West African ancestry or have migrated from there, or from France or Portugal (due to their former colonial connections with West Africa). This means that there may be greater language/communication needs in this patient group than for those with HIV-1.

Clinical practice after diagnosis of HIV-1 has a robust and broad evidence base with clear recommendations around treatment and its positive effects. This is not the case for HIV-2, where there are only limited data on the value of diagnostic tools, monitoring and treatment. Thus, it is very difficult to make recommendations on the basis of high-quality evidence (using the GRADE system). Nonetheless, it can be assumed that general principles will apply. For example, it can be assumed that for those on ART, undetectable = untransmittable (U=U) will apply for people with HIV-2, even though there is no direct evidence. However, it is hard to express the same confidence for those who have an undetectable viral load in the absence of ART. Similarly, much of the good practice and advice around adherence discussed in guidelines for HIV-1 can be assumed to apply for HIV-2 [26]. There are some significant differences between HIV-1 and HIV-2 that are highlighted in these guidelines. These need to be clearly understood and communicated to patients, in the context of involving people in their care and supporting adherence.

3.1 | Testing and diagnosis

Testing for and diagnosis of HIV-2 are more challenging compared with HIV-1. Standard HIV antibody screening tests detect both HIV-1 and HIV-2. This can lead to misunderstandings; people may assume that they have been diagnosed with HIV-1 or not realise that there are different types of HIV, and it may be several weeks before confirmation of HIV-2 is obtained. This can cause uncertainty and confusion.

Likewise, viral load and resistance testing are performed at specialised centres and it takes longer to receive results. HIV-2 groups are so distinct from each other that it is common for resistance tests, and even viral load assays, to fail to amplify which causes further delay in treatment decisions.

3.2 | Treatment

Disease progression of HIV-2 is slower compared to HIV-1. Many people living with untreated HIV-2 have undetectable (or very low) viral loads for many years and may not experience a significant decline in CD4 count. This makes decisions about when to start ART for HIV-2 less clear-cut than for HIV-1. Deferral of treatment with continued monitoring may sometimes be an appropriate course of action for HIV-2, though there are many circumstances (described below) when starting ART is recommended. Nonetheless, in these guidelines we suggest that ART should be routinely offered when a new diagnosis of HIV-2 is made.

Low viral loads may mean that the risk of onward transmission of HIV-2 to sexual partners is significantly lower than for HIV-1. People may have been living with asymptomatic HIV-2 for longer than is usual for HIV-1, but they may still face the same levels of stigma and discrimination.

As well as the complexity of deciding when to start ART, it should be noted that HIV-2 is 'harder to treat' than HIV-1. Most antiretroviral agents were developed for HIV-1 and HIV-2 has intrinsic resistance to some of these drugs. There is some concern about the barrier to resistance and durability of treatment for HIV-2. The limited choice of effective agents also means that there are fewer switch options, and fewer options remaining if resistance develops. This makes adherence a particularly key issue for people living with HIV-2, and more support may be needed. Although peer support organisations can provide invaluable advice about stigma and adherence, the low numbers of people living with HIV-2 in the UK may mean that peer organisations have limited experience of

counselling about HIV-2, its treatment and the lived experience of people with HIV-2. Caution is needed, because information relevant to HIV-1 (for example, on when to start ART, or the option of switching to other antiretroviral drugs to help with side effects) may not be directly translatable to HIV-2.

Treatment for HIV-2 may need to be more closely monitored than for HIV-1, to minimise the risk of resistance developing. There is some evidence to suggest that resistance may develop more easily. The low or undetectable viral loads in people with HIV-2 may mean that CD4 is monitored more frequently in people with HIV-2, compared with HIV-1. The CD4 count might be the most useful marker of health status and response to treatment.

3.3 | General support for people with HIV-2

The differences between HIV-2 and HIV-1, and the resulting uncertainties, mean that more support for people with HIV-2 is needed. Explaining these complexities, particularly immediately after diagnosis when people are emotionally vulnerable, and especially if there are language or comprehension barriers, may be time-consuming and difficult. Although peer support is often advocated at these times, this may need to be more carefully considered or supplemented with additional information in the case of HIV-2, as most of the lived experience in the UK is of HIV-1.

Decisions about when to start ART, and what drugs to start, may need more discussion than might be the case for HIV-1. Given the possible increased risk of developing resistance, special emphasis on adherence may be appropriate, with extra support and more frequent monitoring. There are fewer switch options, so switching because of intolerance to antiretroviral drugs is less of an option than for HIV-1. This may necessitate more support for drug intolerance.

4 | CLINICAL STANDARDS

Recommendation

- We suggest that the BHIVA clinical standards [25] are likely to be appropriate for people living with HIV-2. (Grade 2D)

There is very little research to guide standards for clinical care in HIV-2. From a clinical perspective the same principles as for HIV-1 broadly apply with respect to treatment, monitoring and support. The gaps in our understanding of HIV-2 and its relative rarity suggest that a specialist multi-disciplinary team approach is particularly important. Care should be taken in communicating with other health professionals and people providing support for people with HIV-2 who may have little understanding of the differences compared with HIV-1.

5 | DIAGNOSIS OF HIV-2 INFECTION

5.1 | Laboratory diagnosis of chronic HIV-2 infection

Recommendations

- We recommend that an initial diagnosis of chronic HIV-2 infection should be made using a total of three CE-marked serology tests (i.e. tests conform to EU health and safety requirements) performed in an ISO 15189-accredited laboratory. There must be reactivity in two CE-marked fourth-generation tests for HIV-1 and HIV-2, followed by differentiation of HIV-2 by a third CE-marked antibody-only test. (Grade 1A)
- Clinicians should consider revisiting a previous diagnosis of HIV-1 by repeating HIV-2 serology and molecular tests in individuals with an undetectable HIV-1 viral load in the absence of ART, but a falling CD4 count. This is in order to detect the possibility of missed HIV-1 and HIV-2 dual infection. (GPP)
- Similarly, in those with diagnosed HIV-2 with an undetectable viral load in the absence of ART, clinicians should consider repeating HIV-1 diagnostic tests, if their CD4 count falls. This is to investigate the possibility of HIV-1 superinfection. (GPP)

Rationale

Chronic HIV-2 is the development of persistent infection following the acute phase of primary infection. Accurate testing for HIV-2 chronic infection depends on a laboratory diagnosis, made using at least one venous blood sample. Positive results from tests using other strategies for convenience, such as point-of-care tests (POCTs) or self-sampling and testing schemes, must be followed up with results from a laboratory accredited for HIV testing under ISO 15189 by the UK Accreditation Service (UKAS).

In the UK, the first-line approach to the diagnosis of HIV-2 chronic infection is well established and should follow the HIV-1 and HIV-2 serology pathway presented in the UK Standards for Microbiology Investigation guidance [27].

The approach to patient testing for HIV-2 follows the pathway for HIV-1 diagnosis. A sensitive fourth-generation screening test for HIV-1 and HIV-2 is performed: any samples showing reactivity are subjected to a further two tests,

preferably from separate manufacturers, including one that can differentiate between HIV-1 and HIV-2.

For chronic HIV-2 infection, specific reactivity in all three tests is required to confirm the presence of HIV-2 antibodies in the sample.

As with HIV-1, the patient identity for HIV-2 diagnosis is not confirmed until a second sample from the patient has consistent reactive results. This step is essential to allow for clinic or laboratory errors, which can result in misdiagnosis.

Where a POCT or self-sampling test has been performed prior to the laboratory test, this is considered as one of the two samples. Therefore, one POCT-reactive sample plus one laboratory-reactive sample with differentiation for HIV type is considered adequate for confirmation of identity and HIV-2 infection.

A recently licensed qualitative HIV-1/HIV-2 reverse transcriptase (RT)-polymerase chain reaction (PCR) test may be helpful in confirming the diagnosis of HIV-2 [28].

5.2 | Laboratory diagnosis of acute primary HIV-2 infection

Recommendation

- We recommend that investigation for acute or very recent HIV-2 infection should start as for diagnosis of chronic HIV-2 infection. A negative HIV-2 screening result on a blood sample taken within 3 months of the likely exposure should be further investigated at 6 weeks and 3 months, with parallel testing for HIV-2 viral RNA and, if necessary, HIV-2 proviral DNA. (Grade 1A)

Rationale

Diagnosis of acute primary HIV-2 infection can only be made on the basis of HIV-2 antibody seroconversion.

The need to test for a suspected acute HIV-2 infection is rare [29,30], but the context of managing a needle-stick incident, sexual exposure or other potential transmission event, or clinical presentation, may necessitate consideration of the principles.

Fourth-generation serology tests (see Appendix 2) have become the mainstay of HIV diagnosis, but their development has resulted in bias towards the timely detection of HIV-1 infection. The inclusion of p24 antigen detection in some tests is designed to be specific for HIV-1 only; so in terms of HIV-2 diagnosis, the 'antibody/antigen' test format is solely an antibody test and can justifiably be regarded as equivalent to third-generation tests. A negative result in a screening test must therefore be interpreted with consideration of the 'window' period in which a genuine HIV-2 infection may not be detected by antibody alone.

The window period for HIV-2 antibody detection is considered to be at least as long as for HIV-1. The BHIVA/BASHH/BIA Adult HIV Testing guidelines strongly recommend using a test at a time point at which it has a 99% probability of detecting infection [31]. For third-generation tests, the cumulative probability of a false-*negative* HIV test result is 5%, 1% and 0% by 40, 85 and 99 days post-exposure, respectively [32]. Applying this reasoning to HIV-2 antibody detection, the window period can be established as approximately 90 days from exposure.

HIV-1 avidity tests cannot be used to determine recent HIV-2 infection. The US Food and Drug Administration has approved the Roche cobas® HIV-1/HIV-2 qualitative RT-PCR test for diagnosis, which may be helpful in identifying acute infection [28].

5.3 | Indeterminate HIV-1 or HIV-2 serology: how to investigate further

Recommendation

- We recommend that *any* HIV-1 or HIV-2 serology that does not fit into a clear pattern of a confirmed laboratory diagnosis is fully investigated for the presence or absence of HIV-2 infection, and that this should be established by PCR for HIV-2 proviral DNA. (Grade 1A)

Rationale

Because of the close genetic relationship between HIV-1 and HIV-2, reactivity in combined serological tests may reflect cross-reactivity to either antibody or antigen. Historically, there may also have been some non-specific detection in viral load assays. However, such cross-reactivity should not be considered to indicate that the patient has dual HIV-1 and HIV-2 infection. It is also important to remember that a patient may have had an initial diagnosis of HIV decades previously, when the availability and specificity of diagnostic tests for HIV-2 were not as good as at present.

A fuller investigation of suspected cross-reactive serology should normally include an HIV-2 western blot analysis, to better compare the range of the patient's serological responses to HIV-1 and HIV-2 antigens. Unfortunately, HIV-2 western blot diagnostic tests are not performed in the UK, so the specialist confirmation of HIV-2 infection depends on molecular testing.

The next step on the diagnostic path would normally be an HIV-2 viral load test, but because a significant proportion of patients with HIV-2 do not have a detectable HIV-2 viral load, a negative result can be misleading. Though not quantitative, the Roche cobas® HIV-1/HIV-2 qualitative RT-PCR test has a very low estimated limit of

detection and may be helpful in resolving indeterminate serology or identifying dual infection [28].

If RNA is not detected, the next test to confirm or refute HIV-2 infection in the context of indeterminate serology is investigation for the presence of HIV-2 proviral DNA. This test is more exacting in terms of sample requirement, which must be sent to the laboratory within a relatively short time period because it requires white cells to be separated from whole blood. Nevertheless, the test is capable of reliably and specifically detecting HIV-2 DNA that has been integrated into human lymphocytes.

5.4 | Measuring HIV-2 viral load

Recommendation

- People with HIV-2 should have viral load measured at baseline and then repeated at appropriate intervals (see Section 8 Monitoring). (Grade 1A)

Rationale

Detection of viraemia in HIV-2 varies with time since diagnosis. In studies in West Africa, the proportion of ART-naïve individuals with viral load <50 copies/mL varied between 25% and 40% [33-35]. However, viral load will vary according to time since acquisition and clinical progression as well as between individuals. Measurement of viraemia allows baseline genotypic testing, monitoring of response to treatment or detection of disease progression in those who do not start treatment.

If detectable, the plasma viral load of HIV-2 can be correlated with clinical progression for individual patients [34,36]. A proportion of HIV-2 patients who do not initially have a detectable viraemia may still deteriorate clinically without a newly detectable or increasing plasma viral load. Recommendations for management of these patients are given in Section 5 When to start treatment.

Quantification of HIV-2 subtype B viral load is more problematic than of subtype A, probably due to a relatively wider variation across the viral genome, including the RT-PCR primer-binding sites. This may result in under-quantification, and partly explain the discordance between viral load and clinical progression more regularly observed in subtype B infections.

Almost all methods to measure HIV-2 viral load are based on RT-PCR. These have steadily improved over the years to overcome problems with natural variation in critical primer-binding sites, and limits of both quantification and detection. In addition, almost all HIV-2 quantitative assays are non-commercial 'in-house' tests, although one commercial HIV viral load assay which offers a different methodology is the Cavidi ExaVir assay which measures the polymerase activity of plasma virions. Although the Cavidi ExaVir assay is less sensitive than the better molecular RT-PCR assays (~500 *vs* 100 copies/mL) [37], and cannot distinguish between HIV-1 and HIV-2 load in co-infected patients, it has shown promise in single-sample limited comparisons with RT-PCR assays [38].

Availability of HIV-2 viral load testing is limited in the UK; at the time of writing there are only two diagnostic centres (see Appendix 2 for details). Both centres use methods developed in-house that have been published in peer-reviewed journals, and the development teams are part of the $ACHI_EV_{2E}$ international collaboration (http://etudes.isped.u-bordeaux2.fr/achiev2e/). This collaboration has taken steps to document the variation in assay limits of detection and quantification [37,39], and recommends standards for interpretation of HIV-2 viral load data with relevance to clinical progression [39].

5.5 | Resistance testing

Recommendation

- Resistance testing should be performed at diagnosis, prior to treatment initiation and at virological failure, if the HIV-2 viral load meets the threshold of ≥500 copies/mL. (Grade 1C)

Rationale

Genotypic HIV-2 resistance testing is the only available method for determining drug resistance; there are no phenotypic assays that can be routinely used to inform clinical decisions about treatment. Only one specialist laboratory centre in the UK performs an accredited HIV-2 resistance test (see Appendix 3). Quality assurance is provided by in-house and international schemes.

The limit of HIV-2 viral load for which sequencing can be performed reliably is 500 copies/mL. Prior to requesting HIV-2 resistance testing, the viral load should be determined at one of the two specialist centres providing this assay (see Appendix 3). If the HIV-2 viral load is detected but below the limit of quantification, it may still be possible to attempt resistance testing after discussion with the sequencing laboratory.

The classes of HIV drugs for which resistance testing may be performed are the protease inhibitors (PIs), nucleos(t)ide reverse-transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors (INSTIs). HIV-2 is naturally resistant to all non-nucleos(t)ide reverse-transcriptase inhibitors (NNRTIs), and the fusion inhibitor enfuvirtide (see Section 6 What to start).

The basic methodology for genotypic HIV-2 resistance testing is similar to that used for HIV-1: extraction of viral RNA from plasma, then reverse transcription of RNA to complementary (c)DNA, followed by nested PCR amplification of specific regions of this cDNA. After checking for amplification, the product is then sequenced, scanned for quality of sequence, and analysed for the presence of mutations that are predicted to confer drug resistance [40]. Lists of mutations used in the scanning process are updated regularly and available from international databases and are based on peer-reviewed clinical research [41].

At the time of writing, HIV-2 sequencing is performed using conventional Sanger methodology, which has a limit of sensitivity for point mutations in viral population sequencing of approximately 15%. Thus, any mutations present in a viral population at a proportion less than this are unlikely to be reliably detected, though whether these will have clinical consequences for antiviral control of HIV-2 infection is largely unknown.

6 | WHEN TO START TREATMENT

Recommendations

- It is essential that the risks and benefits of initiating ART are discussed with all individuals with HIV-2. (GPP)
- We suggest that all people with HIV-2 start ART. (Grade 2C)
- We recommend that people with HIV-2 start ART in the following circumstances:
  - If there is dual HIV-1 and HIV-2 infection; (Grade 1A)
  - When a diagnosis is made during primary HIV-2 infection; (Grade 1C)
  - If there is co-infection with hepatitis B (HBV); (Grade 1C)
  - In pregnancy (see Section 9.1 Pregnant women); (Grade 1C)
  - If there is detectable HIV-2 viraemia; (Grade 1B/C)
  - If the CD4 count is below 500 cells/mm^3; (Grade 1B)
  - In advanced HIV disease, or if there are opportunistic infections; (Grade 1B)
  - If there are symptoms, or an indicator condition for HIV-1 and/or HIV-2, regardless of CD4 count or viral load. (Grade 1C)
- We suggest that additional consideration is given to starting ART if there are significant comorbidities. (Grade 2D)

The rationale for these recommendations is considered in detail in the sections below.

6.1 | Chronic infection

Recommendation

- We suggest that people with HIV-2 start ART. (Grade 2C)

Rationale

There are no published randomised controlled trials to determine the optimal timing of ART in HIV-2, limiting the ability of the writing group to make strong recommendations based on high-quality evidence. Existing evidence is largely from cohort studies, which are subject to confounding and are limited by the available ART options at the time the study was performed. In addition, the majority of the large prospective cohort studies recruited participants within West African countries, so generalisability outside of these settings needs to be considered [4,42-45].

There is currently no consensus within national and international guidelines regarding the optimal timing for treatment initiation for people with HIV-2. The US (Department of Health and Human Services) guidelines recommend initiating ART at or soon after HIV-2 diagnosis to prevent disease progression and transmission of HIV-2 to others [46], based partly on extrapolation from HIV-1 studies. Both the World Health Organization (WHO) and European AIDS Clinical Society (EACS) guidelines implicitly include HIV-2 in their recommendations to initiate ART in all adults with HIV [47,48], as does the UNAIDS 90–90–90 target [49]. Other European guidelines take a more nuanced approach, recommending that treatment initiation decisions are based on a combination of CD4 cell count, detectable viraemia and clinical status [14,50-52].

Underpinning many of these considerations is the substantially different clinical course of HIV-2 compared with HIV-1. This is typically characterised by a lower plasma viral load, and slower clinical progression, although the nature of opportunistic infections is indistinguishable and mortality the same as for CD4-matched people with HIV-1 [53-57]. In most settings, the proportion of antiretroviral-naïve individuals presenting with an undetectable viral load is between 25% and 40% [33-35]. However, the evidence base correlating viral load with treatment benefit is very weak. This is largely due to the small proportion of individuals with detectable viral loads available for follow-up [44] and the limited availability of virological monitoring in many of the larger West African cohort study settings [4,42-45]. The results of a cohort study in Caió, Guinea Bissau suggested a strong association between mortality and viral load, with mortality risk over 10 years equal to that of people without HIV for the subgroup of people living with HIV-2 who had undetectable

viral loads at baseline [34]. This study included a larger proportion of older women, and comparison with the study of police officers nationally [4], including a larger proportion of younger men, is difficult because of the population and methodology differences, including lack of viral load data in the latter study. It is also difficult to draw conclusions about survival past 10 years, and about the effects on non-AIDS-related comorbidities among those not on ART.

There is a larger body of evidence correlating CD4 cell count with treatment response, with variable results reported. Several of the larger prospective cohort studies in Europe and West Africa have demonstrated a sustained improvement in CD4 count on treatment when an appropriate ART regimen was used [43,44,58]. A large prospective study, the IeDEA cohort, including individuals with HIV-1 and HIV-2 in settings across five West African countries found a significant increase in CD4 cell count at 12 months among people treated with a PI-based regimen [43]. Immunological recovery was higher among individuals with a lower initial CD4 count (<50 cells/mm^3) [43]. The ACHI$_E$VH$_{2E}$ cohort study, including follow-up of participants from sites in Europe, The Gambia and North America, showed a sustained increase in CD4 counts in individuals who received a PI-based regimen at 12 months of follow-up [44]. Overall, 55% of participants treated with a PI-based regimen met the definition of treatment success (an increase in CD4 count of >50 cells/mm^3 from treatment initiation, with an undetectable plasma RNA in the absence of progression to advanced HIV disease, death or major treatment modification), compared with 10% for those taking three NRTIs.

Immune reconstitution may be slower among people with HIV-2 than among those with HIV-1, despite a higher mean baseline CD4 count [59,60]. An observational cohort study in West Africa showed that, although slower, the difference in CD4 count recovery had equalised between people with HIV-1 and HIV-2 by 24 months, with no difference in overall mortality [59]. However, this finding was not replicated in another observational study using data from the COHERE HIV-1 and ACHI$_E$V$_{2E}$ HIV-2 European cohorts. Here, the mean observed change from treatment start to 12 months was +105 cells/mm^3 in people with HIV-2 and +202 cells/mm^3 in those with HIV-1, with an observed difference between groups of 97 cells/mm^3/year [60]. This effect persisted when adjusted for pre-treatment viral load and ART regimen [60].

Although seen in the larger studies, improvement in CD4 count on treatment is not consistent across all studies, and two small retrospective analyses of UK data demonstrated only a modest gain in CD4 count over time, with some individuals experiencing no change after ART initiation [61,62]. In an observational study comparing outcomes in HIV-1 and HIV-2 in Mali there was also no significant increase in CD4 count on treatment with a PI-based regimen, although this finding was not significantly different from in people with HIV-1 in this study [63].

Of note, the overall evidence suggests that without effective ART, HIV-2 infection will progress to acquired immune deficiency syndrome (AIDS) and death in the majority of individuals, with life expectancy around 10 years shorter among people with HIV-2 than among those without HIV [4]. Data from a prospective occupational cohort study of police officers in Guinea-Bissau showed a longer time to advanced disease and a longer median survival among individuals with HIV-2 than among those with HIV-1 [4]. The finding that people with HIV-2 were more likely to develop clinical AIDS at higher CD4 cell percentages compared with people with HIV-1 (18% *vs* 8%) may be partly explained by the longer periods of time spent with mild or moderate immune suppression, but supports earlier ART initiation [4]. The finding that mortality off-treatment is substantial and that disease progression is similar to but slower than in those with HIV-1, supports universal treatment.

Aside from individual clinical benefit, there was a public health rationale for the change to recommending universal ART for HIV-1 by the WHO in 2015 [47]. ART has been shown to be highly effective in preventing transmission through condomless sex in serodifferent heterosexual couples and men who have sex with men (U=U) [64,65]. It is biologically plausible and likely that the same applies to HIV-2 and this extrapolation formed part of the rationale for this recommendation that all those with HIV-2 start ART. In addition to protecting others, ART for individuals with HIV-2 mono-infection is likely to be protective against new HIV-1 infection. Risk of acquisition of HIV-1 should be assessed, particularly if immediate ART is not planned, and partners tested if possible. New HIV-1 infection has been described in an individual with HIV-2 [66].

The potential benefits of initiating treatment will outweigh the risks in a majority of people, particularly with newer, more tolerable ART options, and detailed discussion on an individual basis is essential. The degree to which asymptomatic individuals with undetectable viral loads and normal CD4 counts will derive benefit from treatment remains unclear and some studies show survival equivalent to people without HIV among individuals with HIV-2 who have undetectable viral loads and normal CD4 counts off ART [34]. On balance, ART is likely to be more beneficial in people with an undetectable HIV-2 viral load and normal CD4 count compared to those with HIV-1 and the same surrogate markers, as progression of disease is

seen in some people with HIV-2 who have undetectable viral loads [67] and immune reconstitution is weaker than in HIV-1 [54], particularly when starting with lower CD4 counts [58]. In addition, existing treatment regimens are generally safe and well tolerated, and there may be secondary benefits of engaging this group in ongoing care, including retention in care.

There are several clinical scenarios in which we make a stronger recommendation to initiate treatment because of evidence of or likely benefit; these are discussed in detail in the sections below.

6.2 | Individuals with dual HIV-1 and HIV-2 infection

Recommendation

- We recommend that people with dual HIV-1 and HIV-2 infection start ART, with a regimen designed to provide full suppression for both viruses. (Grade 1A)

Rationale

Current national (BHIVA) [26] and international (WHO and EACS) [47,48] guidelines recommend that all individuals with HIV-1 start ART, regardless of WHO clinical stage and CD4 cell count. This recommendation is predominantly based on evidence from two large randomised controlled trials designed to evaluate the optimal timing of ART initiation, START [68] and TEMPRANO [69], as well as the HPTN 052 study [65,70] designed to evaluate transmission of HIV-1 from people on ART but with secondary endpoints evaluating clinical benefit of early ART [71]. All three trials demonstrated improved outcomes for morbidity and two showed improvement in mortality when individuals with HIV-1 and CD4 cell counts of >500 cells/mm^3 were randomly assigned to initiate ART immediately compared with delayed initiation. Based on this and the strong evidence for treatment as prevention [64,65,70,72], guidelines worldwide now unanimously recommend universal ART in HIV-1.

The recommendation of early ART for people with HIV-2 is supported by limited evidence from people with HIV-1 and HIV-2 co-infection, with an analysis of the IeDEA group of West African cohorts demonstrating comparable improvements in CD4 cell counts in people with HIV-1, HIV-2 and dual infection following initiation of an effective ART regimen [45]. In a retrospective observational study including 34 people with dual infection living in Spain, 70% of those on appropriate treatment achieved suppression of both viruses after a median 32 months on ART [73].

It is essential to ensure that individuals with dual infection are treated with a regimen designed to provide full suppression of both viruses, and monitoring for virological failure should include viral load and drug resistance testing for both viruses [2].

Additional, limited data suggest that resistance may be more likely to develop in HIV-2 than HIV-1 [73,74], and that managing virological failure in HIV-2 is a challenge due to limited treatment options. For this reason it is worth considering use of a regimen active against both viruses in a scenario in which there is diagnostic uncertainty about the possibility of dual infection or single HIV-2 infection, such as an equivocal antibody test result or while waiting for an HIV-2 viral load result from a reference laboratory.

6.3 | Treatment of primary HIV-2 infection

Recommendation

- We recommend that people diagnosed with HIV-2 during primary HIV-2 infection start ART. (Grade 1C)

Rationale

This recommendation is based on extrapolation from existing evidence for the management of primary infection with HIV-1 [26]. Primary infection is defined as 'HIV infection within a maximum of 6 months from the estimated time of HIV transmission' [26].

Literature searches identified few case reports of individuals presenting with signs and symptoms suggestive of primary infection with HIV-2 [29,75,76]. The presenting clinical symptoms were consistent with those described in primary HIV-1 infection.

Based on extrapolation of relevant literature on HIV-1, we recommend starting ART in primary HIV-2 infection on the basis of:

- Evidence from the TEMPRANO [69], START [68] and HPTN052 [65,70] trials which showed improved mortality and morbidity following initiation of ART, regardless of CD4 cell count, supporting recommendations for immediate treatment;
- Reducing risk of onward transmission at a time of higher viral load [77-81];
- Possible limitation of the viral reservoir to significantly below that seen when treatment is deferred [65,70].

As with all treatment decisions, a detailed discussion regarding the risks and benefits of early treatment initiation is imperative. Given the safety and tolerability of current first-line treatment regimens, it is likely that the potential benefits of initiation will outweigh the risks in the majority of cases. The benefits of engagement and retention in care should also be considered.

6.4 | Individuals with HBV co-infection

Recommendation

- We recommend that all people with HIV-2 who are co-infected with HBV are treated with fully suppressive ART that provides activity against both viruses. (Grade 1C)

Rationale

This recommendation is based on extrapolation from evidence in HIV-1 and HBV co-infection. A literature review did not identify any direct evidence from people with HIV-2 and HBV; however, in West Africa, the prevalence of co-infection with HBV does not appear to vary by HIV type [82,83].

For individuals with HBV mono-infection, recommendations for treatment initiation are based on HBV DNA levels, evidence of liver inflammation and degree of fibrosis [84,85]. The same considerations apply to people with HIV-2 and HBV and particular emphasis should be placed on early ART initiation for those who would independently fulfil criteria for treatment of HBV [26].

Observational evidence from populations with HIV-1 and HBV indicates that co-infection is associated with higher levels of HBV replication and an increased risk of cirrhosis, end-stage liver disease and liver-related mortality [86-90]. Higher HBV DNA levels at baseline appear to be associated with increased mortality [91]. A study in Tanzania demonstrated that HIV-related rather than HBV-related factors are more important contributors to mortality in these individuals [87].

The increased risk of mortality in people with both HBV and HIV-1 co-infection appears to be reduced, but not completely eliminated, by initiation of ART [89,92,93]. One possible explanation for this is a persistently higher prevalence of ongoing HBV viraemia in co-infected people on tenofovir disoproxil fumarate (DF) compared to those with HBV mono-infection [94,95]. The underlying mechanism remains unclear, and signature drug resistance mutations have not been identified [92].

Conversely, hepatitis B surface antigen (HBsAg) loss following treatment initiation appears to be higher in HBV/HIV-1 and is more likely to occur in people with a low baseline CD4 count [92]. One proposed explanation for this is rapid immune reconstitution when ART is initiated in these individuals [92]. Studies of co-infection have shown that HBsAg is lost in up to 22% of people with HIV-1 and HBV, depending on the duration of follow-up [96-98].

Starting treatment in individuals co-infected with HIV and HBV is discussed in the BHIVA guidelines for the management of HIV-1 infection [26].

6.5 | Individuals with a detectable HIV-2 viraemia

Recommendation

- We recommend that people with HIV-2 start ART if there is detectable HIV-2 viraemia. (Grade 1B)

Rationale

We recommend ART for all people with HIV-2 and a detectable viral load for three reasons: to prevent disease progression, to prevent onward disease transmission and to reduce the risk of non-AIDS adverse events.

HIV-2 has a distinct clinical course compared with HIV-1, characterised by a significantly larger proportion of individuals with an undetectable viral load off treatment [33-35]. In most settings, this ranges from 25% to 40% [33-35], compared with 0.15–1.5% for HIV-1 [99]. However, the majority of people with HIV-2 will still experience progression to advanced HIV disease and death if not treated [4]. In addition, evidence suggests that decline in CD4 cell count and clinical progression can occur in HIV-2 in the absence of detectable viraemia [4]. In this context, a detectable viral load should always be treated as significant in a person with HIV-2 and this is a strong indication to initiate ART. The absolute value (copies/mL) would be expected to be lower than for a person with HIV-1 but is still a significant finding and a strong indication for initiating ART. We extrapolate from high-quality evidence in HIV-1 demonstrating a reduction in all-cause mortality with early rather than deferred ART initiation [65,68-70].

Low-level viraemia should not be considered to indicate an absence of risk of adverse outcomes. Plasma viral load values have been shown to be between 10 and 100 times lower in HIV-2 than HIV-1 when matched for CD4 cell count [53]. A cross-sectional analysis of the IeDEA group of cohort studies in West Africa using an ultrasensitive HIV-2 viral load assay with a detection threshold of 10 copies/mL [58] demonstrated that, although at lower values, 47% of individuals off treatment and 35% of those taking ART had a detectable viral load when a lower cut-off value was used. However, it seems there may be disease progression with HV-2 without viraemia: in the French ANRS HIV-2 cohort study, only 17/31 of HIV-2 controllers (55%, 95% confidence interval 37.3–71.5%) were also long-term non-progressors, with others experiencing reductions in CD4 count over time [67].

With the above caveat, cautious comparisons can be drawn between people with HIV-2 and the group of HIV-1 'elite controllers'. This group is most commonly defined as people with HIV-1 who have multiple consecutive undetectable viral load test results for at least 6 months, or undetectable viral load results on at least 90% of measurements

over 10 years [99]. Existing evidence from this group has indicated an increased risk of non-AIDS adverse events compared with people with HIV-1 on ART, even in the absence of a detectable viraemia [100]. A small study using coronary computed tomography angiography showed that HIV-1 elite controllers experienced a higher prevalence of atherosclerosis and markers of immune activation compared to HIV-negative controls [101].

There is strong evidence that people with HIV-1 and an undetectable viral load on ART cannot transmit the virus to their sexual partners [64,65,72]. We extrapolate from evidence in HIV-1 to support the U=U statement and recommend treatment as prevention in HIV-2 [70,71]. Individuals with a detectable HIV-2 viraemia have the potential to transmit infection, and therefore prevention of transmission should be another strong consideration for treatment initiation in this group. The degree to which the absolute value of the HIV-2 viral load correlates with risk of transmission in people with HIV-2 is not known. In people with HIV-1 in the PARTNER2 study, no transmissions occurred with an HIV-1 viral load of less than 200 copies/mL [64,72].

6.6 | Individuals with a CD4 cell count below 500 cells/mm^3

Recommendation

- We recommend ART initiation for all people with HIV-2 with a CD4 cell count below 500 cells/mm^3. (Grade 1C)

Rationale

It is well established that initiating ART is beneficial to people with immunosuppression due to HIV-1 infection. Lower CD4 counts are associated with increased risk of opportunistic infections, and the range of potential pathogens increases as the CD4 count declines. Observational evidence from the pre-ART era indicates that risk of advanced HIV disease is not lower for people with HIV-2 than for those with HIV-1 with the same CD4 counts, and the spectrum of opportunistic disease is indistinguishable [55].

HIV-2 disease progression seems to follow a similar survival curve compared to HIV-1, albeit at a slower rate, and the risk of opportunistic disease may be greater at higher CD4 counts than in HIV-1 [4]. Analyses of observational data from West Africa have repeatedly shown that lower CD4 cell count at ART initiation is significantly associated with higher overall mortality [102,103]. Data from the French ANRS HIV-2 cohort showed that immunological recovery on ART may be less complete among people with HIV-2 than those with HIV-1, supporting early treatment initiation before CD4 counts fall further [45]. Results of the single-arm trial of treatment with elvitegravir-based therapy suggested improved CD4 count increase when starting treatment with >500 cells/mm^3 [104]. Similarly, slow recovery of CD4 counts was shown in a wider European study [60], in a French cohort [105] and in a Gambian cohort [59]. However, one larger prospective cohort study in six West African countries found better CD4 count recovery in patients with lower baseline CD4 counts [42].

These observations may be related in part to suboptimal virological responses, particularly with old ART regimens but, assuming that robust ART regimens are used and monitoring available, good virological response should be achievable.

6.7 | In advanced HIV disease or the presence of opportunistic infections

Recommendation

- We recommend that all people with HIV-2 who have advanced HIV disease or a current or previous opportunistic infection start ART. (Grade 1B)

Rationale

Advanced HIV disease in adults is defined by the WHO as a CD4 count of <200 cells/mm^3 or WHO stage 3 or 4 clinical event at presentation [106].

International guidelines consistently recommended ART in those with symptomatic HIV infection [46,50,51]. Extrapolating from HIV-1, mortality can be high if ART is not started promptly after treatment for opportunistic infections, and the presence of the opportunistic disease or symptoms are markers of immunosuppression and risk of further opportunistic disease. Again extrapolating from HIV-1, ART should be started promptly in the presence of acute opportunistic infections [107] with caution only in central nervous system opportunistic infections, in which very early ART in HIV-1 has been associated with increased adverse events [108,109].

6.8 | In the presence of an indicator condition for HIV

Recommendation

- We recommend that all people with HIV-2 who are symptomatic or have a current or previous indicator condition for HIV start ART. (Grade 1C)

Rationale

Indicator conditions for HIV testing are clinical conditions that are associated with an undiagnosed HIV prevalence of >1/1000 [31,110]. Other than HBV and hepatitis C, which share transmission routes, the key

indicator conditions (for example herpes zoster, bacterial pneumonia and seborrhoeic dermatitis) are markers of immunosuppression and risk of progression to more advanced HIV disease, possibly including in individuals with undetectable HIV-2 viral loads. Indeed, there is some evidence to suggest disease progression in this group [67].

As for the above recommendation (for people with HIV-2 who have advanced HIV disease or a current or previous opportunistic infection), there is no trial evidence to guide recommendations on when to start ART, but there is consensus that symptomatic HIV should be treated.

6.9 | Comorbidities

Recommendation

- We suggest that additional consideration is given to starting ART if there are significant comorbidities. (Grade 2D)

Rationale

In addition to the above considerations, there are other factors that should be considered when discussing initiating treatment in people with HIV-2. Male sex is associated with a higher risk of AIDS, increased rates of loss to follow-up and higher mortality [4,56,102,111]. Additionally, increased age at diagnosis and treatment initiation has been associated with a higher overall mortality [112]. This effect seems to increase as age increases, with age over 45 as a main explanatory factor in some studies [56,112]. Neither of these factors are unique to HIV-2, and similar effects have been seen in people with HIV-1. The limited data on these factors may contribute to discussions about when an individual starts ART.

Comorbidities should also be considered, including a background of significant cardiovascular, renal or hepatic disease. There is no direct evidence linking these diseases with poor prognosis for patients with HIV-2. However, a large randomised trial in patients with HIV-1 showed an increased hazard ratio for significant cardiovascular, renal or hepatic disease events in patients who had received intermittent ART, compared with patients on sustained therapy [113]. It is postulated that this lower risk on therapy could be associated with a reduction in inflammation associated with reduced viraemia.

7 | WHAT TO START

Recommendations

- It is recommended that people with HIV-2 start ART containing two NRTIs plus one of the following: a second-generation INSTI or a ritonavir-boosted PI (PI/r). (Grade 1C)
- Two-drug regimens currently in use for treatment of HIV-1 are not recommended. (Grade 1D)
- NNRTIs are not recommended in the treatment of HIV-2. (Grade 1C)

7.1 | Introduction

There are no published randomised controlled trials of ART in people with HIV-2 infection, thus it is very difficult to make recommendations on the basis of high-quality evidence (using the GRADE system). Almost all the evidence for HIV-2 treatment decisions is from observational data (frequently descriptions of case series or small cohorts). The published studies report limited, if any, data regarding drug-related adverse events, so we rely on extrapolation of data from the HIV-1 literature. Given the absence of comparative trials, it is therefore difficult to balance virological efficacy with the potential for adverse events and adherence issues in relation to different antiretroviral drugs. We expect all salts of tenofovir disoproxil to be active and therefore 'tenofovir DX' is used in the recommendations. Finally, there are no approved drugs to treat HIV-2 and most *in vitro* drug sensitivity and resistance data are derived from group A HIV-2.

7.2 | Which NRTI backbone

Recommendations

- We recommend that tenofovir disoproxil (DX) with emtricitabine is the preferred NRTI backbone. (Grade 1C)
- Tenofovir alafenamide (AF) with emtricitabine is a suggested alternative NRTI backbone if there are clinical reasons to prefer it over tenofovir DX. (Grade 2C)
- Abacavir with lamivudine is another suggested alternative NRTI backbone if there are clinical reasons to avoid both tenofovir prodrugs. (Grade 2D)

Rationale

There are no randomised controlled studies comparing abacavir and lamivudine with tenofovir DX and emtricitabine for the treatment of HIV-2. Much of the published clinical data describe outcomes for individuals treated with zidovudine and lamivudine. Studies using abacavir are generally in the context of triple NRTI treatment with zidovudine and lamivudine [44]. Two non-comparative studies using tenofovir DF and emtricitabine in small numbers of individuals naïve to ART showed a low incidence of drug-related toxicity and good tolerability [104,114]. Tenofovir is preferred over abacavir owing to the

likelihood of greater activity of the former in the presence of viral resistance, with some evidence of success using tenofovir DF/emtricitabine in second-line treatment, including in a patient with the Q151M RT mutation [115].

Tenofovir AF is a prodrug of tenofovir that yields lower plasma concentrations of free tenofovir. In the context of HIV-1 it has been shown to have less negative impact on bone and renal markers [116]. Although published clinical data regarding its use are extremely limited [73], *in vitro* data show that tenofovir AF has potent activity against HIV-2 [117]. We therefore suggest tenofovir AF/emtricitabine as an alternative backbone for initial therapy.

7.2.1 | Not recommended

Zidovudine and stavudine are not recommended as first-line treatment for HIV-2 due to mitochondrial toxicity, and didanosine is similarly not recommended due to mitochondrial and hepatic toxicity.

7.3 | Which third agent

Recommendations

- We recommend that therapy-naïve individuals start ART containing dolutegravir or darunavir/r as the preferred third agent. (Grade 1C for both)
- Bictegravir is a suggested alternative INSTI if clinically appropriate. (Grade 2D)
- Cobicistat is an alternative pharmacokinetic enhancer if clinically appropriate. (Grade 2D)
- Raltegravir is a suggested alternative INSTI if clinically appropriate. (Grade 2C)
- Cobicistat-boosted elvitegravir is a suggested alternative INSTI if clinically appropriate. (Grade 2C)
- We suggest that lopinavir/r should be reserved for those who cannot tolerate either darunavir/r or dolutegravir or when there are clinical reasons to avoid the other third agents listed above. (Grade 2C)

Rationale

7.3.1 | Dolutegravir

There is limited clinical experience in the use of dolutegravir in ART-naïve people with HIV-2. A retrospective study of 12 subjects starting dolutegravir-based therapy with HIV-2 viral load of <100 copies/mL resulted in a median CD4 cell count increase of 272 cells/mm^3 at 18 months from a pre-treatment baseline of 591 cells/mm^3. Those who were tested maintained an HIV viral load of <100 copies/mL [118]. Dolutegravir, dosed twice daily, also appears to retain activity in those with previous raltegravir experience and first-generation INSTI resistance [119-121]. This is consistent with *in vitro* observations that dolutegravir has higher potency against HIV-2 than first-generation INSTIs [122]. Dolutegravir is therefore recommended as a potent, tolerable INSTI in the first-line treatment of HIV-2. No data exist on the optimal dose of dolutegravir in the treatment of HIV-2. However, given the potential for resistance development and limited treatment options, we consider that 50 mg twice daily should be used. If an individual is consistently aviraemic prior to starting treatment, use of the 50 mg once daily dose can be considered.

There are no head-to-head comparisons of darunavir/r with dolutegravir to help decide whether one should be preferred over the other. However, clinicians may wish to take into account the likelihood of better tolerability of dolutegravir as well as the reduced potential for drug–drug interactions.

7.3.2 | Darunavir/r

There are no data comparing different ritonavir-boosted PIs in the treatment of HIV-2. Saquinavir/r, lopinavir/r and darunavir/r have all been associated with treatment response [123-126], and have good *in vitro* activity against HIV-2 [5]. There are limited clinical data regarding the use of daranuvir/r in treatment-naïve individuals. Darunavir/r is recommended on the basis of a better tolerability and toxicity profile in HIV-1 infection compared to saquinavir/r and lopinavir/r. No data exist on the optimal dosing of darunavir/r in the treatment of HIV-2. However, given the potential for resistance development and limited treatment options, we consider that darunavir 600 mg/ritonavir 100 mg twice daily should be used. If an individual is consistently aviraemic prior to starting treatment, the darunavir 800 mg/ritonavir 100 mg once daily dose may be considered.

7.3.3 | Bictegravir

Bictegravir is highly potent *in vitro* against HIV-2 although there are no published data on the clinical use of bictegravir in individuals with untreated HIV-2 infection [127]. Bictegravir is only available in a single tablet containing emtricitabine and tenofovir AF. It is not possible to increase the dose of bictegravir alone, which is potentially a disadvantage in treating individuals with HIV-2 with a detectable viral load, or a past history of treatment failure on an INSTI. The published clinical experience

with tenofovir AF as mentioned above is limited to small numbers of cases.

7.3.4 | Cobicistat

There are no published data regarding the use of cobicistat in combination with darunavir in the treatment of treatment-naïve individuals with HIV-2 infection. Its use as a pharmacokinetic enhancer of the INSTI elvitegravir as initial therapy in 30 subjects as part of the fixed-dose combination of tenofovir DF/emtricitabine/cobicistat/elvitegravir showed good tolerability [104]. Note that cobicistat is not an appropriate booster for use in twice daily dosing.

7.3.5 | Raltegravir

Raltegravir has been shown to provide good treatment outcome in a non-comparative French study (30 participants) in combination with tenofovir DF/emtricitabine [114]. HIV-2 viral load was greater than or equal to 40 copies/mL in 20 participants at baseline and below 40 copies/mL at week 48 in 96% of study participants. In this study, raltegravir was given twice daily. There are no data on the use of once daily raltegravir in HIV-2. The durability of first-generation INSTIs when used to treat HIV-2 is uncertain; however, in one retrospective study, the use of raltegravir was associated with relatively frequent emergence of INSTI mutations [73].

7.3.6 | Elvitegravir/c

A single-arm study investigated the use of the fixed-dose combination of tenofovir DF/emtricitabine/elvitegravir/cobicistat [104] in 30 people with HIV-2 in Senegal. HIV-2 viral load was <50 copies/mL in 25 of the 30 (83%) subjects at baseline and in 28 (93%) subjects at week 48. The combination was well tolerated and adherence was good. *In vitro* data indicate that HIV-2 integrase gene amino acid substitutions associated with raltegravir resistance confer cross-resistance to elvitegravir [128].

7.3.7 | Not recommended

HIV-2 has reduced phenotypic sensitivity to the PIs atazanavir, fosamprenavir and tipranavir compared with HIV-1 and these drugs should not be used [123,124]. HIV-2 exhibits intrinsic resistance to the NNRTI class of drugs due to the differing structure of the NNRTI-binding pocket in HIV-2 compared to HIV-1 and these drugs should not be used [129-131]. It is also likely that HIV-2 is intrinsically resistant to the fusion inhibitor enfuvirtide [131]. HIV-2 R5 tropic virus is sensitive *in vitro* to maraviroc, however there is no clinical experience of maraviroc use in treatment-naïve individuals [132]. An HIV-2 genotypic tropism prediction tool is available [133].

8 | HIV-1 AND HIV-2 CO-INFECTION

Recommendations

- Consider the viral load and resistance profiles for both viruses when selecting treatment. (GPP)
- We recommend that, if there is a clinical reason to start treatment before a definitive diagnosis is made, treatment is started as for HIV-2 using twice daily dosing of either dolutegravir or boosted darunavir. (Grade 1D)

Rationale

The serological diagnosis of dual infection with HIV-1 and HIV-2 can be difficult (see Section 4. Diagnosis of HIV-2 infection). This is particularly true if the HIV-2 viral load is undetectable. In general, the recommended treatment for HIV-2 will successfully treat HIV-1, with the possible exception of the unusual circumstance of multi-drug class transmitted drug resistance. If the CD4 count is very low or there is another reason to start treatment before all diagnostic and baseline information is available, the higher dose of the third agent is likely to provide a margin of safety around the choice of treatment.

9 | MONITORING

Recommendations

- In individuals who are not on treatment, CD4 cell counts should be measured at 3- to 6-month intervals depending on the baseline value and rate of decline of CD4 count. (Grade 1B)
- In individuals who are not on treatment, the viral load should be measured at baseline and every 6 months. (Grade 1C)
- Baseline testing for NRTI, PI and INSTI resistance should be performed prior to starting ART; a sample should be retained if resistance testing is not possible. (Grade 1C)
- In those who are taking ART, the CD4 cell count should be measured at 1, 3 and 6 months after starting or

changing ART and 3–6 monthly thereafter depending on the nadir CD4 cell count. (Grade 1C)
- If the pre-treatment viral load was detectable, the viral load should be measured at 1, 3 and 6 months after starting or changing ART and then 3–6 monthly. (Grade 1C)
- If the pre-treatment viral load was undetectable, the viral load should be measured at 1 month and then 6 monthly. (Grade 1C)
- The HIV-2 viral load should be repeated in those on ART when it has been maximally suppressed and then becomes detectable. (Grade 1D)
- Testing for drug resistance should be performed in those on ART when the HIV-2 viral load has been maximally suppressed and then becomes repeatedly detectable. (Grade 1C)

Rationale

For guidance regarding monitoring and frequency of non-HIV-specific tests in people living with HIV-2, refer to the BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals [134]. These guidelines outline the assessment and investigation of individuals at different stages of HIV care. There is limited evidence to inform guidance on monitoring in HIV-2 [14,50].

The following factors need to be taken into account when determining the frequency and timing of HIV-specific tests: immunological and virological differences between HIV-1 and HIV-2, such as different rates of disease progression and CD4 cell count decline; the proportion of ART-naïve individuals with undetectable viral load, CD4 cell count increase and viral load reduction in response to treatment; and time to develop resistance in individuals with HIV-2 on treatment.

In individuals with HIV-2 the rate of CD4 cell count decline is slower compared to those with HIV-1, with an annual average CD4 cell count loss of 11 compared to 49 cells/mm^3/year [54]. Therefore, asymptomatic individuals with CD4 cell counts of >500 cells/mm^3 who have decided to defer treatment may undergo 6-monthly monitoring if their CD4 cell decline is slow. CD4 cell count response to first-line treatment is poorer in HIV-2 compared to HIV-1, particularly at lower CD4 cell counts [60]. More frequent CD4 cell count monitoring may therefore be needed in those commencing treatment, particularly if the nadir CD4 cell count is low.

In individuals with HIV-2 not taking ART the viral load is lower compared to untreated individuals with HIV-1 and is more often undetectable. In the IeDEA West African collaboration 46% of untreated individuals had a viral load of <10 copies/mL using an in-house ultrasensitive HIV-2 RNA assay [135]. Viral load estimation may therefore be of limited clinical utility in monitoring the response to ART or identifying treatment failure. A fall in CD4 count may be the only indication of treatment failure. Closer CD4 cell count monitoring may therefore be needed in this context.

Transmitted drug resistance in HIV-2 has been reported in 5% of untreated people living with HIV-2 in France [136]. A baseline genotypic resistance test (protease, reverse transcriptase and integrase genes) should be performed on the earliest available sample in order to exclude transmitted drug resistant mutations because mutations can disappear when drug pressure is removed on changing ART.

Virological response to ART is slower in individuals with HIV-2 with log reductions of –0.62 compared to −1.56 log/mL/month in those with HIV-1 [50], therefore more frequent viral load monitoring should be considered to ensure adequate treatment response, particularly as HIV-2 develops resistance to ART more quickly than HIV-1 in the presence of detectable viral load [137].

A resistance test should be performed at the time of virological failure and preferably within 4 weeks of stopping or changing ART to guide future ART choices.

10 | PREGNANT WOMEN AND NEONATAL POST-EXPOSURE PROPHYLAXIS

10.1 | Pregnant women

Recommendations

- We recommend that pregnant women with HIV-2 should initiate ART, if they are not already established on an effective regimen. (Grade 1C)
- We recommend that an effective ART regimen already established at conception should be continued. (Grade 1C)
- We recommend tenofovir DX with emtricitabine as the preferred NRTI backbone. (Grade 1C)
- We recommend darunavir/r as the preferred third agent. (Grade 1C)
- Dolutegravir may be used or continued as a preferred third agent, taking into consideration the possible risks and benefits for the woman. (Grade 1C)
- Case discussion with experts with experience of managing HIV-2 is recommended for all pregnant women. (Grade 1D)
- Women with HIV-2 who wish to conceive should be informed about the possible risks associated with dolutegravir use around the time of conception. (GPP)

Rationale

An effective ART regimen already established at conception should be continued [138]. It is reasonable to extrapolate data regarding maternal and fetal drug safety from HIV-1 to HIV-2 [14].

For women who are not already taking ART, the risks and benefits of treatment initiation should be discussed in detail and advice taken if needed from a specialist with experience of managing HIV-2. Where treatment is initiated during pregnancy, tenofovir DX and emtricitabine is the preferred NRTI backbone. This should be used with darunavir/r as the third agent as clinical experience using ritonavir-boosted PIs in pregnant women is greater than with INSTIs [139]. It is suggested that the darunavir 600 mg/ritonavir 100 mg twice daily dose should be used [140]. Dolutegravir may be used as the third agent in pregnancy from 6 weeks' gestation, following guidance in HIV-1 [138]. If considering the use of dolutegravir and in women of childbearing potential, the data relating to the use of dolutegravir should be discussed, as in other guidance [138,141]. Clinicians should bear in mind that the choices for women with HIV-2 are limited and the third agents recommended as the safest options in HIV-1 (efavirenz and boosted atazanavir) are not suitable for women with HIV-2 [138].

The risk of vertical transmission of untreated HIV-2 is lower than in HIV-1 but is not zero. Data from the pre-HAART (highly active anti-retroviral therapy) era indicate a transmission risk of between 0.6% and 4.0% [139,142-144]. One small study of 15 pregnant women with HIV-2 in Burkina Faso with three transmissions estimated a 29.5% risk of vertical transmission in HIV-2, but this is inconsistent with findings from much larger studies [145].

Limited data exist on the efficacy of ART in preventing vertical transmission in HIV-2, mainly due to the low numbers of transmissions. Data from the French ANRS perinatal cohort did not show a reduction in vertical transmission following the introduction of ART [139]. However, in the one case of transmission post-ART that occurred in 2002, there had been incomplete adherence to ART in pregnancy and a detectable HIV-2 viral load of 800 copies/mL [139]. Data from a prospective cohort study in Portugal indicated a possible reduction in vertical transmission of HIV-2 when effective interventions to prevent transmission were used [146].

The absence of a detectable viral load should not be used as a factor to delay treatment initiation, as HIV-2 transmission may have occurred in this situation [139]. Zidovudine monotherapy has been used for the prevention of vertical transmission in women with HIV-2, but the observational data are not of high enough quality to make a definitive recommendation for its use, as in HIV-1 [138]. Initiating ART when an individual has an undetectable viral load may additionally prevent complications should the viral load become detectable later in pregnancy.

Women who conceive on ART that is not fully suppressive or lose virological control during pregnancy should be managed as outlined in the BHIVA guidelines for the management of HIV in pregnancy and postpartum [138]. ART intensification if required should be with an INSTI [131]. There are other circumstances in which clinicians should consider changing an effective ART regimen in pregnancy; these are discussed in detail in the BHIVA guidelines for the management of HIV in pregnancy and postpartum [138].

For detailed information on the timing of treatment initiation in women not taking ART, refer to the BHIVA guidelines for the management of HIV in pregnancy and postpartum [138].

Pregnant women who initiate ART should be advised to continue therapy lifelong. This may improve retention in care, which is often poor in people living with HIV-2.

10.2 | Neonatal post-exposure prophylaxis

Recommendations

- Infants who are defined as being at very low or low risk of vertical transmission should receive zidovudine monotherapy. (Grade 1D)
- We suggest that the duration of zidovudine monotherapy should be 2 weeks and 4 weeks for very low-risk and low-risk infants, respectively, stratified as per the BHIVA HIV-1 pregnancy guidelines. (Grade 2D)
- Infants who are defined as being at high risk of vertical transmission should receive triple therapy with zidovudine/lamivudine/raltegravir. (Grade 1D)

Rationale

Although data are lacking, infants born to women living with HIV-2 who are defined as being at very low or low risk of vertical transmission according to HIV-1 pregnancy guidelines should be managed as for HIV-1 with regard to neonatal post-exposure prophylaxis (PEP) [138]. There is no evidence to guide practice with regard to infants born to women living with HIV-2 who are defined as at high risk of vertical transmission. In this situation three-drug PEP should be used with raltegravir as the third agent. As noted in the BHIVA HIV-1 pregnancy guidelines [138], in high-risk situations, lopinavir/ritonavir can be used with caution as the third agent. Expert advice should be sought on neonatal PEP in babies born to women living with HIV-2.

For detailed information about neonatal PEP, refer to the BHIVA guidelines for the management of HIV in pregnancy and postpartum [138].

11 | TREATMENT OF CHILDREN LIVING WITH HIV-2

There is no evidence to guide treatment of children and it is unlikely that a substantial body of evidence will ever exist. This document can guide treatment, but the choice of agents will be guided by criteria such as age and the availability of appropriate formulations. Given the rarity of this situation, discussion at a national multidisciplinary team meeting would be appropriate. For more information, please refer to the PENTA guidelines, taking into account the differences in drug susceptibility for HIV-2 [147].

12 | MANAGING TREATMENT FAILURE

Recommendations

- Genotypic resistance testing should be attempted in the event of virological rebound. (Grade 1C)
- Algorithmic resistance mutation analysis should be utilised if resistance is detected. (Grade 1D)
- We suggest that specialist advice is sought from a clinician with experience in managing HIV-2. (Grade 2D)
- Fully active agents should be used to construct a second-line regimen in the case of resistance, though it may be necessary to continue partially active agents in order to maximise overall regimen activity. (Grade 1D)

Treatment failure is poorly defined in HIV-2 as much of the published research includes individuals starting treatment with an undetectable viral load or where monitoring of treatment response was performed using change in CD4 cell count alone. The CD4 cell count response to first-line treatment in HIV-2 is lower than in HIV-1 contributing to the difficulty in assessing treatment response in individuals with HIV-2 [60]. Virological rebound with treatment-emergent resistance is well described and [121,148-150] rates of treatment failure to first-line ART are high in cohorts from Africa and Europe. Overall, 33% of individuals treated with a boosted PI in the $ACHI_EV_{2E}$ collaboration study did not reach a composite 12-month endpoint of CD4 cell count increase of ≥50 cells/mm^3 from treatment initiation, with undetectable plasma RNA in the absence of progression to AIDS or death [44].

A definition of treatment failure in HIV-2 has therefore been suggested which takes into consideration these issues. Treatment failure can be defined as: detection of HIV-2 plasma RNA in at least two consecutive tests; decline in CD4 cell count; and/or persistence or emergence of HIV/AIDS-specific symptoms [14].

The activity of individual agents, alone and in combination, in second-line treatment is also poorly understood, being heavily reliant on *in vitro* data.

It is particularly important to identify any barriers to adherence as this may be the main cause of virological rebound. There are a limited number of active drugs available if genotypic resistance develops. Proactive treatment switching to more tolerable drugs may be particularly important in the setting of virological rebound with no detectable resistance as adherence factors are likely to play a significant role [33].

Genotyping should be attempted if the viral load is high enough (≥500 copies/mL) and used to inform treatment selection (see Section 4.5 Resistance testing). The HIV2EU group has published HIV-2 resistance mutations and an online mutation analysis algorithm is available to help interpret genotype results [151].

Drugs that may yield additional activity against HIV-2 include NRTIs such as zidovudine [152] and the CCR5 co-receptor inhibitor maraviroc. In the case of the latter agent, it is likely that HIV-2 uses the co-receptors CCR5 and CXCR4 *in vivo*, though less efficient use of other co-receptors has been demonstrated *in vitro* [153,154]. R5 tropic viruses have shown sensitivity to maraviroc *in vitro* and while R5-tropism prediction algorithms are available, v3 loop sequencing is not routinely available in the UK [132,155].

The HIV2EU mutation list interpretation algorithm is available at: http://www.hiv-grade.de/HIV2EU/deployed/grade.pl?program=hivalg&action=showMutationForm.

13 | PEP AND PRE-EXPOSURE PROPHYLAXIS FOR SEXUAL EXPOSURE TO HIV-2

Recommendation

- We suggest that PEP after sexual exposure and pre-exposure prophylaxis (PrEP) used for HIV-1 are likely to be effective against HIV-2. (Grade 2D)

There is no evidence to inform use of PEP or PrEP in HIV-2. It is biologically plausible that current regimens used in the UK are effective. If PEP is used after confirmed exposure to HIV-2, follow-up HIV testing should take account of the longer window period for serological tests.

14 | AUDITABLE STANDARDS

Most centres will provide care for small numbers of people living with HIV-2, so targets in terms of meeting these standards for a percentage of individuals are not given. Any care episode for which the following recommendations are not met should prompt investigation including root cause analysis if indicated.

1. People with a new diagnosis of HIV-2 should have viral load measured at baseline.
2. HIV-1 co-infection should be excluded by antibody testing at baseline.
3. For all those with detectable HIV-2 RNA, resistance testing should be attempted at baseline.
4. Resistance testing should be attempted if there is virological failure.
5. ART should be recommended to all those with a CD4 count <500 cells/mm^3, and all those with detectable viraemia.
6. ART should be recommended to all those with symptomatic HIV-2, opportunistic infections or HBV co-infection.
7. Currently recommended antiretroviral regimens should be used in people starting ART for HIV-2, with PIs or INSTIs as core agents.

We recommend that management of pregnant women with HIV-2 is audited alongside the management of pregnant women with HIV-1 infection, taking into account the different ART regimens recommended for people living with HIV-2.

Similarly, we recommend that monitoring for people with HIV-2 is audited alongside that for people living with HIV-1, taking into account any slight differences in viral load measurement, confirmation of treatment failure and resistance testing.

15 | LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BASHH	British Association for Sexual Health and HIV
BHIVA	British HIV Association
BIA	British Infection Association
cDNA	Complementary DNA
EACS	European AIDS Clinical Society
EIA	Enzyme immunoassay
GPP	Good practice point
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAART	Highly active anti-retroviral therapy
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
INSTI	Integrase strand transfer inhibitor
NICE	National Institute for Health and Care Excellence
NNRTI	Non-nucleos(t)ide reverse-transcriptase inhibitor
NRTI	Nucleos(t)ide reverse-transcriptase inhibitor
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PI	Protease inhibitor
POCT	Point-of-care test
PrEP	Pre-exposure prophylaxis
RT-PCR	Reverse transcriptase-polymerase chain reaction
SIV	Simian immunodeficiency virus
SIVsmm	Simian immunodeficiency virus of sooty mangabeys
Tenofovir AF	Tenofovir alafenamide
Tenofovir DF	Tenofovir disoproxil fumarate
Tenofovir DX	Tenofovir disoproxil
UKAS	UK Accreditation Service
WHO	World Health Organization

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APPENDIX 1

Summary of the modified GRADE system

BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [1,2].

1A Strong recommendation. High-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Consistent evidence from well-performed, randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Strong recommendations, can apply to most individuals in most circumstances without reservation. Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.	2A Weak recommendation. High-quality evidence. Benefits closely balanced with risks and burdens. Consistent evidence from well-performed randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Weak recommendation, best action may differ depending on circumstances or individuals or societal values.
1B Strong recommendation. Moderate-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Evidence from randomised controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk. Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.	2B Weak recommendation. Moderate-quality evidence. Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens. Evidence from randomised controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise). Further research may change the estimate of benefit and risk. Weak recommendation, alternative approaches likely to be better for some individuals under some circumstances.
1C Strong recommendation. Low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence from observational studies, unsystematic clinical experience or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain. Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.	2C Weak recommendation. Low-quality evidence. Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens. Evidence from observational studies, unsystematic clinical experience or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain. Weak recommendation; other alternatives may be reasonable.
1D Strong recommendation. Very low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence limited to case studies. Strong recommendation based only on case studies and expert judgement.	2D Weak recommendation. Very low-quality evidence. Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens. Evidence limited to case studies and expert judgement. Very weak recommendation; other alternatives may be equally reasonable.

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APPENDIX 2

Successive generations of HIV-2 serology tests

Generation of HIV test	Description
First	Based on viral lysate antigens to detect HIV antibodies (e.g. western blot)
Second	Utilise synthetic peptide or recombinant protein antigens with/without viral lysates to detect HIV immunoglobulin (Ig)G antibodies
Third	Synthetic peptide or recombinant protein antigen-based tests detect IgM and IgG antibodies with increased sensitivity during early seroconversion
Fourth	Combination third-generation assays to detect IgM and IgG antibodies, and monoclonal antibodies to detect p24 antigen
Fifth	Detect and distinguish between HIV-1/HIV-2 antibodies and p24 antigen in the same sample

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APPENDIX 3

Laboratory tests and assays relevant to HIV-2

Test	Utility for HIV-2 diagnosis and monitoring	Location	Specialist provider
HIV-1 and HIV-2 antibody/antigen	Screening test or part of confirmation; detects HIV-2 antibody only	Local laboratory; confirmation often performed at reference centre	Local large NHS Trust; Public Health England (PHE) regional laboratory
HIV-1 or HIV-2 antibody typing	Part of confirmation; detects HIV antibody with differentiation of HIV-2	Confirmation often performed at reference centre	Local large NHS Trust; PHE regional laboratory
Qualitative plasma HIV-2 RNA	Presence or absence of HIV-2 RNA; helpful in establishing diagnosis with inconsistent serology	Specialist centre	Health Services Laboratories [1]
Quantitative plasma HIV-2 RNA	HIV-2 RNA viral load; used for monitoring patients who have detectable plasma viral load	Specialist centre	Barts Health [2], Health Services Laboratories [1]
HIV-2 resistance	Identifies known mutations predicted as conferring antiviral drug resistance	Specialist centre	PHE Birmingham [3]
HIV-2 proviral DNA	Integrated HIV-2 genome in cells; establishes diagnosis when serology is inconclusive and HIV-2 RNA undetectable	Specialist centre	Health Services Laboratories [1]

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