Review Article

Recommendations for the use of antiretroviral therapy in adults living with human immunodeficiency virus in Singapore

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Abstract

Since the advent of combination antiretroviral therapy (ART), the mortality attributable to human immunodeficiency virus (HIV) infection has decreased by 80%. Newer antiretroviral agents are highly efficacious, have minimal side effects as compared to older drugs, and can be formulated as combination tablets to reduce patients' pill burden. Despite these advances, 680,000 people worldwide died of acquired immunodeficiency syndrome-related illnesses in 2020. The National ART and Monitoring Recommendations by the National HIV Programme have been created to guide physicians on the prescribing of ART based on the patients' needs. These recommendations are based on international guidelines and tailored to the local context and unique domestic considerations. We hoped that with the publication of these recommendations, the care of people living with HIV can be enhanced, bringing us closer to ending HIV in our lifetime.

Keywords: ART, HIV, recommendations

INTRODUCTION TO HUMAN IMMUNODEFICIENCY VIRUS AND ANTIRETROVIRAL THERAPY

The treatment of human immunodeficiency virus (HIV) infection has come a long way from its initial description as the cause of the acquired immunodeficiency syndrome (AIDS) in 1981. This progress has transformed a formerly fatal disease to a chronic, though not yet curable, disease. Since the advent of combination antiretroviral therapy (ART), the mortality attributable to HIV infection has decreased by 80%.[1,2] Newer antiretroviral agents (ARVs) are highly efficacious, have minimal side effects as compared to older drugs, and can be formulated as single-table combination regimens, reducing the pill burden experienced by patients.

In addition to improving the mortality and morbidity of individuals living with HIV infection, treatment is also crucial for preventing the onward transmission of HIV. Treatment as Prevention (TasP) refers to the use of ART to prevent HIV transmission and is one of the key strategies in the ambitious goal to end HIV globally. Evidence for TasP comes from large trials that collectively confirm that people living with HIV who have sustained undetectable viral loads (<200 copies/mL) while on ART have effectively no risk of transmitting HIV.

The first of these trials was the HIV Prevention Trials Network (HTPN) 052 trial, wherein 1763 serodiscordant couples were enrolled from nine countries and randomised to receive either early or delayed ART. The couples enrolled

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consisted of heterosexual men and women, men who have sex with men (MSM) and women who have sex with women. Early ART was associated with 93% risk reduction in linked partner infections.[3] This finding was echoed in the PARTNER2 and Opposites Attract studies, which focused largely on MSM couples.

During the 76,991 condomless sex acts in the PARTNER2 study, the rate of within-couple HIV transmission in serodiscordant MSM couples (with the HIV-positive partner receiving suppressive ART) was 0.23/100 couple-years of follow-up. There were no phylogenetically linked partner transmissions.[4] In the Opposites Attract study, 343 serodiscordant MSM couples were enrolled. Following 16,800 acts of condomless penetrative sexual intercourse observed in the study, no phylogenetically linked HIV transmission was observed.[5]

Despite these advances, 680,000 people worldwide died of AIDS-related illnesses in 2020.[6] In recognition of the morbidity and mortality associated with HIV, in 2016, the United Nations Member States issued a historic declaration to end AIDS by 2030. One of the key targets necessary to achieve this goal is having less than 500,000 new HIV infections globally by 2020. Since then, the number of new HIV diagnoses has continued to fall, but at a pace far slower than what is required to achieve the ambitious aim of ending AIDS by 2030.[7]

The Joint United Nations Programme on HIV/AIDS aims to end the epidemic by achieving the 90–90–90 targets by 2020: 90% of all people living with HIV will know their diagnosis; 90% of all people diagnosed with HIV infection will receive ART; and 90% of all people receiving ART will achieve durable viral suppression.[8] As of 2020, 80% of people in Singapore who had HIV infection were aware of their serostatus; 91% of these were receiving treatment and 91% of those on ART had achieved durable viral suppression.[9] While these findings are promising, more can be done to increase HIV testing rates, and we should continue to make an effort to encourage people living with HIV to initiate and remain on therapy.

The National ART and Monitoring Recommendations by the National HIV Programme have been created to guide physicians on the prescribing of ART based on patients' needs. These recommendations are based on international guidelines and are tailored to the local context and unique domestic considerations. It is hoped that with the publication of these recommendations, the care of people living with HIV can be enhanced, bringing us closer to the goal of ending HIV in our lifetime. For clarity and ease of understanding, we will be referring to our recommendation as 'the national recommendations' in this article.

WHAT'S NEW IN THE RECOMMENDATION

1. **Cost considerations**

   Sixteen antiretroviral agents have been included in the subsidised drug list as of 1 September 2020. This change greatly reduces the cost of antiretroviral therapy (ART) for patients, including dolutegravir (DTG)-based regimens.

2. **Selection of ART**
   - Bictegravir (BIC)- and DTG-based regimens are now recommended as first-line regimens in view of the numerous advantages they have over non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. This is due to evidence of increasing NNRTI resistance and the inclusion of DTG in the subsidised drug list, making integrase strand transfer inhibitor-based regimens increasingly affordable [Tables S1–S3, Supplemental Digital Appendix].
   - The nucleoside reverse transcriptase inhibitor-sparing regimen DTG/lamivudine has been included as a first-line regimen, with caveats [Table S3, Supplemental Digital Appendix].
   - The NNRTI-based regimens have now been moved to alternative first-line regimens [Tables S1 and S2, Supplemental Digital Appendix].
   - Atazanavir/ritonavir has been removed from the alternative first-line regimen under protease inhibitor-based regimen.

3. **Switching ART in the setting of virological suppression**
   - Two-drug regimens have been added as part of the strategy for switching ART regimens [Table S4, Supplemental Digital Appendix].
   - Increased emphasis has been placed on the switching of nevirapine-based regimens to other regimens (either within class or cross-class switch).

4. **Monitoring**
   - Cytomegalovirus IgG is no longer required as part of baseline serologies for all newly diagnosed patients with HIV infection.
   - Toxoplasma antibody should be checked for all newly diagnosed patients with HIV infection. If cost is a concern, physicians may opt to check it only for individuals with CD4 cell count <100 cells/mm^3.
   - Serum cryptococcal antigen should be checked for individuals with CD4 cell counts <100 cells/mm^3.

SECTION 1: INTRODUCTION

Section 1: Key points

Antiretroviral therapy (ART) should be started for all individuals within 2 weeks of presentation to care, barring these exceptions:

1. Tuberculosis (TB): We recommend that ART should be started within 2 weeks of TB treatment initiation for patients with CD4 count <50 cells/mm^3, but within 2–8 weeks of TB treatment initiation if the CD4 count is ≥50 cells/mm^3.
2. Cytomegalovirus retinitis (CMVR): The optimal timing of ART initiation should be individualised. Joint management by an HIV physician and an ophthalmologist with expertise in managing CMVR is required.
3. Central nervous system opportunistic infections (OIs): We recommend that ART should be delayed in patients with central nervous system OIs until specific treatment for these OIs has been initiated and clinical improvement is observed.

1.1 When to start ART?

Antiretroviral therapy should be started as soon as the diagnosis of HIV infection is made. This recommendation is based on the findings of two landmark trials, TEMPRANO and ART-START, which demonstrated approximately 50% reduction in mortality and morbidity when patients who had CD4 counts >500 cells/mm^3 were randomised to receive ART immediately versus delayed initiation (when ART was started once the CD4 counts declined to 350 cells/mm^3).[10,11] Numerous studies have also demonstrated that starting ART within 1 week to 1 month of diagnosis slows disease progression, reduces the size of the viral reservoir, decreases the risk of treatment failure and improves immune recovery.[11-14] In line with these findings, we also recommend that ART should be started in all people living with HIV infection within 2 weeks of presentation to care.

Many acute opportunistic infections (OIs), such as cryptosporidiosis and progressive multifocal leukoencephalopathy, have no specific effective treatments, and initiation of ART is crucial for immune reconstitution, which will in turn, improve disease outcomes. In addition, early initiation of ART is associated with increased survival with several OIs such as *Pneumocystis* pneumonia.[15] However, ART should be delayed in the settings of the specific OIs discussed below.

1.2 Tuberculosis

In general, multiple trials have shown that ART should not be delayed until completion of tuberculosis (TB) treatment. Early initiation of ART in patients with TB has been shown to be associated with improved mortality and reduced risk of OIs. This was demonstrated in the SAPIT trial, which showed a relative reduction of 56% in mortality in the group that had early initiation of ART, although the incidence of immune reconstitution inflammatory syndrome (IRIS) was also significantly higher in this group.[16] This is likewise supported by the CAMELIA and ACTG A5221 trials.[17,18] The CAMELIA trial demonstrated a hazard ratio of death of 0.62 in the early ART initiation group compared to the delayed ART group, with a higher risk of clinically apparent immune reconstitution in the early ART group.[17]

1.3 Cytomegalovirus retinitis

Although there are no randomised controlled trials (RCT) to guide the optimal timing of ART initiation in patients diagnosed with cytomegalovirus retinitis (CMVR), there is a risk of CMVR-IRIS resulting in blindness in patients who are not treated for CMVR before starting ART. Hence, care should be taken to ensure that treatment for CMVR has been initiated before starting ART.

1.4 Central nervous system opportunistic infections

Early initiation of ART in patients with cryptococcal meningitis or TB meningitis may result in serious complications due to IRIS, and some trials have demonstrated an association between increased mortality and early ART initiation.[19,20] In these cases, a short delay before initiating ART should be considered. In the setting of central nervous system TB, if ART is initiated within 2–8 weeks, careful monitoring for IRIS is required. In the setting of cryptococcal meningitis, ART initiation should be delayed until completion of the induction phase of antifungal therapy, and possibly until after consolidation therapy depending on the clinical context.[21]

SECTION 2: ART SELECTION

2.1 Principles of ART selection

Most international guidelines recommend ART regimens based on the following guiding principles:[22-25] effectiveness of the ART regimen, safety profile, barrier to resistance, dosing frequency, pill burden, drug–drug interactions and considerations of specific coinfections or other comorbid conditions. Likewise, the general principles for ART selection in the local context are based on the aforementioned principles. In addition, cost-effectiveness is an important consideration to ensure sustained universal access to ART in Singapore.

Singapore uses a copayment model in ART financing, with some of the cost of treatment being borne by the patient. Since 1 September 2020, majority of the ARTs have been included in the national subsidised drug list, making the cost of ART increasingly affordable.[26] All eligible patients (Singapore residents) who purchase any of the 16 drugs on the list will now receive 50%–75% worth of subsidies, depending on the patient's means testing outcomes.[26,27]

Section 2: Key points

1. The inclusion of most antiretroviral therapies (ARTs) in the national subsidised drug list from 1 September 2020 has made the treatment of HIV increasingly more affordable.
2. Dolutegravir (DTG)- and Bictegravir (BIC)-based regimens are the preferred first-line regimens [Tables S1–S3] , Supplemental Digital Appendix. These include the following:
   - Tenofovir disoproxil fumarate (TDF)- or tenofovir alafenamide (TAF)/emtricitabine (FTC)- or lamivudine (3TC)-based regimens, combined with DTG. BIC is currently only available as a combination tablet with TAF/FTC (Biktarvy®).
   - Abacavir (ABC)/3TC-based regimens: A combination tablet consisting of ABC, 3TC and DTG is available (Triumeq®).
   - Nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens: DTG/3TC
   - Raltegravir (RAL)-based regimens are no longer recommended as first-line regimens.
3. Non-nucleoside reverse transcriptase inhibitor (NNRTI)- and darunavir/ritonavir (DRV/r)-based regimens can be considered as alternative first-line regimens if integrase strand transfer inhibitor (INSTI)-based regimens cannot be used.
4. Tenofovir-containing regimens:
   - TDF-containing regimens should be avoided in individuals with creatinine clearance (CrCl) <60 mL/min.
   - TAF-containing regimens should be avoided in individuals with CrCl <30 mL/min.
5. ABC-containing regimens:
   - HLA B*57:01 testing before the use of ABC is only necessary for non-Chinese patients, including lndian and Malay patients, with late-stage HIV infection (CD4 <200 cells/mm^3) [Table S4, Supplemental Digital Appendix].
   - ABC should be avoided in patients with high cardiovascular risk or in those with a documented history of ischaemic heart disease.
   - ABC should be avoided in individuals with a pretreatment viral load of ≥100,000 copies/mL, except when combined with DTG. The combination of ABC/3TC should also be avoided in individuals with HIV–hepatitis B virus (HBV) coinfection. If ABC/3TC must be used in these individuals, an additional HBV-active agent, such as entecavir, should be added.
6. The ART choice for ART-naïve patients is shown in Box 1 [see Supplemental Digital Appendix].

However, there may still be certain groups of patients for whom the cost of ART presents a significant burden. For instance, among the first-line regimens recommended, BIC is not included in the subsidised drug list. A study conducted in the United States reported that increased cost sharing is associated with lower rates of drug treatment, reduced adherence and frequent discontinuation of therapy.[28] Hence, it is prudent for physicians to discuss these concerns with their patients and minimise patients' out-of-pocket expenses as much as they can.

It is still important not to compromise clinical outcomes while minimising patients' expenses. One way to reduce the overall cost borne by patients is to optimise and rationalise laboratory monitoring. For instance, it has been shown that while CD4 cell count monitoring is useful in the first 48 weeks of treatment, patients who have otherwise responded with HIV-1 RNA <50 copies/mL and rise in CD4 count ≥ 200 cells/mm^3 do not appear to benefit from further CD4 cell count testing overall.[29] Another laboratory test that can be rationalised in the local setting is testing for the HLA B*57:01 allele. While international guidelines advise that HLA B*57:01 testing should be performed before using ABC, a study conducted in Singapore showed that HLA-B*5701 testing is only cost effective in Malay and Indian patients with late-stage HIV infection (see section 2.7, subsection 'Abacavir').[30] Hence, the decision to perform this test before initiation of ABC-containing regimens should be made on a patient-to-patient basis.

2.2 Integrase strand transfer inhibitor regimens

The INSTI-based regimens are recommended as first-line regimens in most international guidelines in view of their superior efficacy, improved tolerability, infrequent drug–drug interactions, excellent safety profiles and availability as single-tablet combination formulations.[22-25] Compared to NNRTI-based regimens, INSTI-based regimens also have higher genetic barrier to resistance. In view of the increasing trend of NRTI and NNRTI resistance globally, the World Health Organization (WHO) has also recommended dolutegravir (DTG)-based regimens as the first-line regimen in adults and children.[31] Singapore's transmitted drug resistance data were provided to National HIV Programme by the National Public Health Laboratory during the National HIV Programme ART workgroup retreat. This increasing trend of drug resistance among patients who were newly diagnosed with HIV infection has also been seen locally. In Singapore, the prevalence of overall transmitted drug resistance has increased from 3.8% in 2018 to 7.1% in 2019 and 6.0% in 2020. Likewise, the prevalence of NNRTI-transmitted drug resistance has increased from 2.3% in 2018 to 5.4% in 2019 and 4.6% in 2020. In addition, the inclusion of DTG in the subsidised drug list has made INSTI-based regimens increasingly affordable.[27] Hence, in view of the aforementioned advantages and drug resistance trends, the national recommendations also recommend DTG- and BIC-based regimens as the first-line regimens. Raltegravir (RAL)-based regimens are not listed as first line because RAL has a lower genetic barrier to resistance as compared to DTG and BIC.[32,33] Elvitegravir (EVG), which is usually coformulated with cobicistat, has many significant

drug interactions, which limits its ease of use. It is not widely available in Singapore, and therefore it is not included in the national recommendations.

Compared to efavirenz (EFV)-based regimens, DTG has been shown to result in higher rates of virological suppression and is better tolerated with fewer discontinuations due to side effects. The SINGLE trial, a randomised, double-blind, Phase 3 study comparing ABC/3TC/DTG versus TDF/FTC/EFV once daily in treatment-naïve patients with HIV-1 infection showed that a higher proportion of patients achieved an HIV viral load of <50 copies/mL when receiving ABC/3TC/DTG when compared to TDF/FTC/EFV in week 144, meeting the criteria for superiority.[34] In addition, the proportion of patients who discontinued therapy due to adverse reactions was significantly lower in the ABC/3TC/DTG group compared to the TDF/FTC/EFV group.[34] Rash and neuropsychiatric events were more commonly seen in the TDF/FTC/EFV group, although the incidence of insomnia was higher in the group receiving DTG.[34] Drug resistance mutation was not detected in the ABC/3TC/DTG group, while one TDF-associated mutation and four EFV-associated mutations were detected in the participants with virological failure in the TDF/FTC/EFV group.[34]

Likewise, in comparison to protease inhibitors (PI), DTG is associated with fewer adverse events and increased tolerability. This was demonstrated in the FLAMINGO trial, which was a 96-week, multicentre, open-label, Phase 3b, non-inferiority trial in which treatment-naïve patients with HIV-1 infection were randomly assigned to receive DTG 50 mg once daily or DRV 800 mg plus ritonavir (RTV or/r) 100 mg (DRV/r) once daily in combination with either TDF/FTC or ABC/3TC. Thirteen participants in the DRV/r group discontinued because of adverse events, in comparison to six participants in the DTG group. Fewer adverse events were observed in the DTG group compared to the DRV/r group.[35]

However, despite these advantages in comparison to NNRTI- and PI-based regimens, there have been reports of weight gain and neuropsychiatric side effects (NPSEs) specific to INSTI-based regimens. Sax *et al*.[36] reported that INSTI use was associated with more weight gain compared to PI or NNRTI use, with DTG and BIC being associated with more weight gain compared to EVG. Although DTG has significantly less NPSEs compared to EFV-based regimen, significant symptoms of insomnia and sleep disorders are still being reported.[34,37] These adverse effects are not absolute indications to cease DTG-based therapy, and physicians should discuss with patients regarding their preferences before making a decision on switching therapies.

There are also concerns that DTG-based regimens may be associated with an increased risk of neural tube defects (NTDs) when used at the time of conception.[38] In view of this, several international guidelines previously recommended that DTG be avoided in women who wish to conceive.[22-25] However, other studies (including the ADVANCE study in South Africa) have shown no higher rates of adverse pregnancy outcomes with the use of DTG.[39] Similar findings were also noted in a Brazilian study, where 382 HIV-positive women who were exposed to DTG at conception were compared to 1086 women exposed to either EFV or RAL. Neural tube defects were not noted in either the DTG-exposed group or the group receiving EFV or RAL.[40] In view of this, WHO released a statement in July 2019 recommending the use of DTG as a preferred first-line and second-line treatment for all HIV-infected individuals, including pregnant women and women of childbearing potential.[41] Providers should discuss the benefits of using DTG and the risk of NTDs, and allow the patient to make informed decisions about care, if there is a chance that they may conceive during this time.[22] In line with this, we recommend DTG-based regimens to be used as part of the first-line regimen for all HIV-infected individuals, including women of childbearing potential [Tables S1–S3, Supplemental Digital Appendix].

Bictegravir, which is combined with TAF and FTC as a single tablet called Biktarvy®, is also recommended as a first-line regimen. Since the last national recommendations, BIC is now widely available in most restructured hospitals. It has been recently approved by the US Food and Drug Administration (FDA) for use in treatment-naïve individuals with HIV-1 infection, as well as in patients who are virologically suppressed for at least 3 months with no history of treatment failure and no known resistance mutation to the individual components of TAF/FTC/BIC. Evidence for its use came from studies 1489, 1490, 1844 and 1878. Study 1489 is a double-blind, multicentre, non-inferiority RCT comparing TAF/FTC/BIC (coformulated as a single tablet) versus ABC/3TC/DTG (coformulated as a single tablet) for 144 weeks. At the end of 48 weeks, the BIC group was non-inferior to the DTG group in terms of virological suppression, with no emergent drug resistance.[42] In addition, BIC was well tolerated with better gastrointestinal tolerability, compared to DTG.[42] This finding of non-inferiority in virological suppression was also seen when TAF/3TC/BIC was compared to TAF/3TC/DTG in Study 1490, while the rates of adverse events were similar.[43]

The other advantage of BIC-based regimen is that unlike ABC/3TC/DTG, TAF/3TC/BIC does not require HLA B*57:01 testing, as it does not have the ABC component, making it suitable for rapid or same day initiation of therapy. In addition, TAF can be used in the treatment of HBV infection, making it a convenient option for patients' coinfection with HIV-1 infection and hepatitis B.[44]

However, unlike ABC/3TC/DTG, TAF/FTC/BIC is not included in the subsidised drug list, making this regimen significantly more costly than DTG-based regimens.[27] The BIC-based regimens are also associated with weight gain.[36] In a pooled analysis of eight RCTs in ART-naïve individuals, the

weight gain observed between DTG- and BIC-based regimens was similar.[36] There is also limited data concerning the use of BIC around the time of conception and pregnancy; therefore, it should not be used in individuals who are pregnant or planning for pregnancy until more data are available. In view of these factors, TAF/FTC/BIC should only be considered as a first-line regimen in individuals who cannot use ABC/3TC/DTG or DTG/3TC (such as individuals with HBV coinfection) and in individuals for whom cost is not a significant consideration.

2.3 Nucleoside reverse transcriptase inhibitor-sparing regimens

Two-drug regimens, which typically do not contain a dual-NRTI backbone, can potentially reduce long-term cumulative drug exposure and decrease treatment-associated cost for patients. In addition, some patients may not be able to tolerate NRTI due to underlying premorbid conditions (such as chronic kidney disease, ischaemic heart disease or presence of the HLA B*57:01), making NRTI-sparing regimens attractive alternatives. The main drug in an NRTI-sparing regimen needs to have a high potency and a high barrier to resistance, making DTG well suited for inclusion in such a regimen.

Moreover, DTG/3TC has been studied in the GEMINI-I and GEMINI-II trials. A total of 1433 ART-naïve participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomised to receive DTG/3TC versus TDF/FTC/DTG. At week 96, DTG/3TC was non-inferior to TDF/FTC/DTG in virological suppression, with 86% of participants in the DTG/3TC group and 89.5% of participants in the TDF/FTC/DTG group achieving viral loads <50 copies/mL.[45] This was sustained through week 144, with 82% of participants in the DTG/3TC group and 84% of participants in TDF/FTC/DTG group maintaining viral loads <50 copies/mL. Virological nonresponse was also uncommon, occurring in 3.1% of participants in the DTG/3TC group and 2% of participants in the TDF/FTC/DTG group.[45] No instance of emergent INSTI or NRTI resistance was seen in both treatment groups.[45] A reduced incidence of adverse drug events was found in the DTG/3TC group compared to the TDF/FTC/DTG group, although the increase in weight gain (1.8% in DTG/3TC group and 1.4% in TDF/FTC/DTG group) was comparable in both groups.[45]

In view of the above, several international guidelines have included DTG/3TC as the first-line regimen for individuals with HIV RNA <500,000 copies/mL and no evidence of HBV-coinfection. Likewise, the national recommendations also recommend DTG/3TC as a first-line regimen for these individuals. However, while DTG/3TC is formulated as a single combination tablet known as Dovato®, this formulation is currently not widely available in Singapore. Physicians should note that individuals who are on this regimen will have a higher pill burden compared to individuals on other DTG-based regimens.

2.4 Non-nucleoside reverse transcriptase inhibitor-based regimens

Efavirenz has a long track record of use with high potency. It can also be used for patients who require antitubercular treatment as dose adjustment of rifampicin and EFV is not required, although 400 mg dose of EFV is not recommended in this clinical context. However, it is associated with significant NPSEs, which may result in more toxicity-related treatment discontinuations. In view of this, most international guidelines have designated EFV-based regimens as alternative regimens for use in certain clinical situations where INSTIs cannot be used.[22-25] Despite these disadvantages, NNRTI-based regimens were still retained as first-line regimens in the 2019 national recommendations as the costs of NNRTI-based regimens were significantly lower than those of INSTI-based regimens in the local context. However, with the inclusion of DTG in the subsidised drug list, the cost of INSTI-based regimens has now become less of a concern. In consideration of the significant NPSEs compared to INSTI-based regimens, NNRTI-based regimens are now moved to alternative first-line therapy in the national recommendations.

Efavirenz remains a highly potent ARV, despite recent RCTs demonstrating the superiority of DTG in achieving virological suppression. It is non-inferior to PIs, such as boosted atazanavir/r (ATV/r), when used in combination with either ABC/3TC or TDF/FTC.[46] In patients with significant NPSEs due to EFV, the dose of EFV can be reduced to 400 mg instead of 600 mg. This dosing has been shown in the ENCORE 1 trial to be non-inferior in terms of virological suppression to the standard dosing of 600 mg, with significantly fewer adverse events observed in the 400 mg dosing group as compared to the 600 mg group.[47] We recommend the use of EFV in patients who do not have significant neuropsychiatric history and for whom the cost of INSTI-based regimens is still a concern [Tables S1 and S2, Supplemental Digital Appendix]. In patients with significant NPSE on EFV-based regimens, the dose of EFV can be reduced to 400 mg instead of 600 mg.

Rilpivirine (RPV) has also been recommended as an alternative regimen if INSTI regimens cannot be used.[22,23] Rilpivirine-containing regimens are considered as alternative regimens in many guidelines, as its use is associated with increased risk of treatment failure in cases where the pretreatment HIV viral load exceeds 100,000 copies/mL and pretreatment CD4 count is <200 cells/mm^3. This is seen in the ECHO and THRIVE trials, as well as the STar trial, where it is found to be non-inferior to EFV only if pretreatment HIV viral load is <100,000 copies/mL.[48,49] In addition, for optimal absorption, it needs to be taken with meals comprising at least 390 calories, and coadministration with proton-pump inhibitors (PPIs) must be avoided. Rilpivirine demonstrated better tolerability than EFV in both trials, especially when comparing NPSEs.[48,49] However, given the

caloric requirements, RPV may not be suitable for patients who have irregular meal timings or are fasting. In view of this, we recommend the use of RPV-based regimen only if the pretreatment HIV viral load is <100,000 copies/mL and the pretreatment CD4 count is >200 cells/mm^3 in individuals who cannot use INSTI-based regimens [Tables S1 and S2, Supplemental Digital Appendix].

Doravirine (DOR) has been included in many international recommendations as an alternative first-line regimen. It is a novel NNRTI that retains activity against viruses containing the most frequently transmitted NNRTI mutations, such as K103N, E138K, Y181C and G190A.[50] The efficacy of DOR-based therapy has been studied in two randomised, double-blind, placebo-controlled trials. In the DRIVE-AHEAD trial, 734 ART-naïve participants were randomised into TDF/3TC/DOR versus TDF/FTC/EFV groups. At 96 weeks, the TDF/3TC/DOR group was non-inferior to the TDF/FTC/EFV group, with 77.5% of participants in the DOR arm and 73.6% of participants in the EFV arm achieving viral load <50 copies/mL.[51] More participants in the EFV arm compared to the DOR arm discontinued their assigned ART because of adverse events. Rash and NPSEs were more common in the EFV arm.[51] In the DRIVE-FORWARD trial, DOR has also been compared against DRV/r; in the trial, 769 ART-naïve individuals were randomised to receive DOR versus DRV/r combined with either TDF/FTC or ABC/3TC. At week 96, DOR was found to be non-inferior to DRV/r, with 73% of participants in the DOR group and 66% of participants in the DRV/r group achieving HIV RNA <50 copies/mL.[52] The rate of virological failure was also similar between the two groups, with more participants in the DRV/r arm experiencing treatment-related diarrhoea and poorer cholesterol control.[52] Doravirine has not yet been compared to INSTI. However, DOR is currently not widely unavailable in Singapore, and hence is not included in the recommendations.

2.5 Deciding between NNRTI- and INSTI-based regimens

In 2019, the national recommendations included both NNRTI-based regimens and INSTI-based regimens as first line despite the advantages that INSTI-based regimens have over NNRTI-based ones. At the time of developing the 2019 national recommendations, ARVs were not included in the national subsidised drug list and INSTI-based regimens were significantly more expensive than NNRTI-based regimens. After the inclusion of 16 ARVs in the subsidised drug list, NNRTI-based regimens still remain cheaper than INSTI-based regimens in the local context, although the cost difference between the two has been significantly narrowed. As such, NNRTI-based regimen has been moved from a first-line regimen to an alternative first-line regimen.

As described previously, DTG-based regimens are virologically more efficacious, are better tolerated and have a higher genetic barrier to resistance.[34] In contrast, EFV-based regimens are associated with prominent NPSEs and have a lower genetic barrier to resistance. Thus, RPV cannot be used if the pretreatment HIV viral load is >100,000 copies/mL, as it is associated with more virological failures[48,49] and has to be taken with meals, without which there may be reduced drug absorption, leading to increased risk of treatment failure. In addition, RPV cannot be coadministered with PPIs.

The combination of TDF/FTC (or 3TC)/EFV has a low genetic barrier to resistance as all three component ARVs require only a single base pair substitution each to result in drug resistance (K65R for TDF, M184V for FTC or 3TC, and K103N for EFV). In patients who are non-adherent to this regimen, virological failure is most commonly associated with the development of treatment-emergent EFV and 3TC resistance.[53] In addition, mutations often confer cross-resistance within the class. For instance, K103N confers resistance to EFV as well as nevirapine (NVP), while M184V confers resistance to 3TC, FTC and low-level resistance to ABC.[54,55] Likewise, RPV also has a low genetic barrier to resistance, with the most common treatment-emergent resistance mutation being E138K, which can also confer resistance to etravirine.[56] In essence, future ARV choices can become significantly restricted through the acquisition of treatment-emergent mutations.

The superiority of DTG-based regimens over EFV-based regimens has been established in a meta-analysis by WHO, which showed improved viral suppression, fewer discontinuations overall and fewer discontinuations due to adverse effects in DTG-based regimens when compared to EFV-based regimens.[57] Although DTG and EFV 400 mg can only be compared indirectly in this meta-analysis, there is evidence to suggest that DTG leads to fewer discontinuations and better long-term viral suppression. In view of this, DTG-based regimens have been considered first-line regimens in the latest iteration of the WHO HIV treatment guidelines.[57]

It is important to note that resistance to NNRTIs is more likely to develop in the setting of non-adherence. Efavirenz has been shown in numerous studies to be highly efficacious with durable viral suppression and no treatment-emergent mutations in patients who are highly adherent.[46,53] The same virological efficacy has also been demonstrated in RPV if the pretreatment HIV viral load is <100,000 copies/mL.[48,49] While our local transmitted resistance to NNRTI among newly diagnosed patients is below the 10% threshold defined by WHO as high prevalence (which would necessitate the use of a non-NNRTI regimen as first line), the prevalence of local transmitted drug resistance to NNRTI has been steadily rising in the last few years, from 2.3% in 2018 to 4.6% in 2020.[58]

Despite its various advantages over EFV-based therapy, DTG has been associated with significant weight gain and other NPSEs such as insomnia and sleep disorders.[36,37]

Moreover, EFV- or RPV-based regimens are less costly than DTG-based regimens. As Singapore uses a copayment model for ART financing, the higher cost of DTG may still present an economic burden for some patients despite its inclusion into the subsidised drug list, and this may, in turn, negatively affect adherence to therapy.[28] Hence, in consideration of all the aforementioned points, we recommend NNRTI-based regimen as an alternative first-line therapy. When deciding between an NNRTI or INSTI-based regimen, physicians should take into account factors such as patient preference, cost, comorbid conditions and tolerability [Tables S1 and S2, Supplemental Digital Appendix].

2.6 Protease inhibitors-based regimens

The PI-based regimens have been removed from all international guidelines as first-line regimens, as they have many disadvantages compared to the aforementioned regimens.[22-25] As they are potent hepatic cytochrome P450 3A4 enzyme inhibitors, they are associated with significant drug–drug interactions compared to INSTI- and NNRTI-based regimens. In addition, they are less well tolerated than INSTI-based regimens and may be less efficacious in certain drug combinations. For these reasons, PI-based regimens are listed as alternative first-line regimens in the national recommendations.

If PI-based regimens must be used, we prefer the use of DRV-based regimens over ATV (coadministered with RTV as a pharmacological booster). In a trial by Sax *et al.*,[59] it was found that in patients who were on ABC/3TC and either ATV/r or EFV, the time to virological failure was significantly shorter with ATV/r compared to that with EFV if the initial HIV viral load was >100,000 copies/mL. For this reason, similar to EFV, ATV/r can only be used with ABC/3TC if the pretreatment HIV viral load is <100,000 copies/mL.

DRV/r was compared to ATV/r and RAL in the open-label, Phase 3 ACTG 5257 trial, wherein all three drugs were used in combination with TDF/FTC. While the virological efficacy was similar with all three agents, DRV/r demonstrated improved tolerability compared to ATV/r. Overall, however, RAL was superior to both PIs in terms of a composite endpoint of virological efficacy and tolerability.[60] This was also seen in the FLAMINGO trial, where a DTG-based regimen was superior to DRV/r-based regimen in terms of both virological efficacy and tolerability at 48 weeks.[61] Hence, in consideration of the aforementioned points, PI-based regimens should be used as an alternative first-line regimen if an NNRTI-based or an INSTI-based first-line regimen cannot be used [Tables S1 and S2, Supplemental Digital Appendix]. If a PI-based regimen is used, DRV/r is recommended over all other PIs.

2.7 Nucleoside reverse transcriptase inhibitors

The recommended NRTI agents that form the backbones of combination ART are TDF/FTC and ABC/3TC, both of which are available as single-tablet combinations. As generic TDF is now more widely available, some clinicians may choose to use TDF and 3TC as separate agents to save cost. This combination is not available as a single-tablet combination.

Tenofovir: TDF and TAF

The two main concerns with the use of TDF are renal and bone toxicities. The use of TDF has been associated with new-onset or worsening renal impairment.[62] This risk is noticeably higher among females, and in patients with lower body weight, pre-existing renal impairment and using a PI-based regimen.[63,64] In addition, TDF has been associated with a decline in bone mineral density (BMD), especially when compared to ABC.[65] Cases of osteomalacia have also been reported with TDF use.[66,67] The mechanism of bone loss is believed to be related to the development of proximal renal tubulopathy secondary to TDF use, resulting in phosphate loss and progression of osteomalacia.[67] In view of this, most international guidelines advise that TDF-containing regimens should be avoided in individuals whose CrCl is <60 mL/min.[22-25] Likewise, the national recommendations also agree that TDF-containing regimens should be avoided in individuals whose CrCl is <60 mL/min.

Tenofovir alafenamide is a prodrug of tenofovir and is available as TAF/FTC (formulated as a combination tablet called Descovy®) or in combination with BIC (formulated as a combination tablet called Biktarvy®). Compared to TDF, TAF has reduced potential for adverse kidney and bone effects. This was seen in a double-blind trial, where treatment-naïve adults were randomised to receive TAF or TDF combined with EVG. At 144 weeks, TAF had less impact than TDF on BMD and renal biomarkers.[68] No participants had to discontinue TAF due to renal adverse effects, in comparison to TDF.[68] This observation was also noted in other trials.[69,70] The same benefits were also noted when switching from TDF- to TAF-based regimen. In a randomised, multicentre, open-label study where patients were switched from TDF-based regimens to TAF-based regimens, improved BMD and renal function was noted among patients who were switched to TAF-based regimens.[71] Some studies reported significant weight gain among individuals on TAF-based regimens as compared to TDF-based regimens, but the clinical significance of this finding is still unclear.[36,72] As there are limited data on the use of TAF in patients with CrCl <30 mL/min, most international guidelines have advised avoiding the use of TAF in these patients. Likewise, we also recommend that TAF should be avoided in individuals with CrCl <30 mL/min. Despite the advantages of TAF-based regimens compared to TDF-based regimens, TAF-based regimens (e.g. TAF/FTC/BIC) are still significantly more costly than TDF-based regimens in the local context. Hence, TDF-based regimens remain the first-line regimen for individuals who require tenofovir use but have significant cost concerns [Tables S1 and S2, Supplemental Digital Appendix].

Abacavir

One of the main concerns with the use of ABC is the risk of a hypersensitivity reaction, which has been observed in 5%–8% of individuals who started ABC in clinical trials before the introduction of HLA B*57:01 testing.[73] In view of this, most international guidelines advise that HLA B*57:01 testing should be performed before the use of ABC.[22-25] A study conducted in Singapore to evaluate the cost-effectiveness of such an approach in the local setting showed that the HLA B*57:01 allele frequency in the Chinese, Malay and Indian populations was 0.26%, 2.44% and 15.10%, respectively.[30] In the study, late-stage HIV infection was defined as a CD4 count <200 cells/mm^3. Genotyping before ABC use was not found to be cost effective in early-stage HIV infection for patients of all ethnicities. However, it was cost effective in late-stage infection for HIV-infected individuals of Malay and Indian ethnicities.[30]

Prescribers should take into account other data from Asia suggesting that HLA B*57:01 is optional only in those of Han Chinese ethnicity.[74] Moreover, it should be noted that in a small minority of patients (<1%), a clinical syndrome similar to ABC hypersensitivity reaction may still be possible despite a negative HLA B*57:01 test result.[75] Hence, in contrast to international guidelines, the national recommendations suggest HLA B*57:01 testing before the use of ABC only for non-Chinese patients, including Indian and Malay patients, with late-stage HIV infection (CD4 <200 cells/mm^3) [Table S5, Supplemental Digital Appendix], and that the decision to test before initiation of treatment be made on a patient-by-patient basis.

An association between ABC use and myocardial infarction was first noted in the D:A:D study, where exposure to ABC was associated with an increased risk of myocardial infarction in the first 6 months after initiation of the drug.[76,77] Some other trials also replicated this finding.[78,79] However, there are some studies that did not show this association, including a US FDA meta-analysis of 26 trials that evaluated ABC.[80,81] As such, no clear conclusion can be made about the association of ABC and myocardial infarction. Most international guidelines advise that ABC be avoided if patients are at high risk for cardiovascular disease.[22-25] Patients' risk of developing cardiovascular illness may be predicted with cardiovascular disease risk calculators, such as the Framingham general cardiovascular Risk Score.[82] However, it is important to note that not all risk calculators have been validated in HIV-infected populations. We also recommend that ABC be avoided in patients with high cardiovascular risk or in those with a documented history of ischaemic heart disease.

As mentioned in sections 2.4 and 2.6, ABC has reduced virological efficacy compared to TDF if the pretreatment viral load is ≥100,000 copies/mL. In the ACTG 5202 study, an RCT with more than 1800 participants, the efficacy of ABC/3TC and TDF/FTC was compared when used with either EFV or ATV/r. In patients with a pretreatment viral load ≥100,000 copies/mL, the time to virological failure is significantly shorter in the ABC/3TC group, regardless of the third active agent.[59] The exception to this rule is if ABC/3TC is combined with DTG. This was seen in the SINGLE trial, where a higher proportion of patients achieved an HIV viral load <50 copies/mL when receiving ABC/3TC/DTG as compared to TDF/FTC/EFV in week 144.[34] Also, ABC cannot treat HBV infection, and the use of 3TC alone in HIV–HBV coinfection has been associated with 3TC resistance in HBV.[83] Thus, ABC should be avoided in individuals with a pretreatment viral load ≥100,000 copies/mL, except when combined with DTG. The combination of ABC/3TC should also be avoided in individuals with HIV–HBV coinfection. If ABC/3TC must be used in these individuals, another HBV-active agent such as entecavir should be added.

Comparing ABC/3TC versus TDF/FTC

A comparison was made between TDF/FTC and ABC/3TC in the ACTG 5202 trial, an RCT with >1800 participants where the efficacy and safety of TDF/FTC and ABC/3TC with either EFV or ATV/r were compared. In patients with baseline HIV viral load >100,000 copies/mL, there was a significantly shorter time to virological failure with ABC/3TC as compared to TDF/FTC, regardless of whether the third active drug was EFV or ATV/r.[46] In patients with HIV viral load >100,000 copies/mL, the combination of ABC/3TC with EFV should be avoided.

SECTION 3: SWITCHING ART REGIMENS IN THE SETTING OF VIROLOGICAL SUPPRESSION

Section 3: Key points

1. The national recommendations recommend that patients should be virologically suppressed for at least 6 months before considering switching ART regimens.
2. The follow strategies can be employed when switching ART regimens in the setting of virological suppression [Tables S4–S7, Supplemental Digital Appendix]:
   - Switching NRTI backbone
   - Switching the third drug
   - Switching from older single-tablet fixed-dose combinations to a combination tablet
   - Switching from a three-drug to a two-drug regimen
3. Physicians should switch out patients on NVP-based therapy to another regimen (either within-class or cross-class switch) in view of its unacceptable side effects, pill burden and decreasing cost of other ARVs.
4. If patients are unable to tolerate NRTI-based regimens, physicians can consider using a two-drug regimen instead [Table S4]. Possible combinations that can be used include DTG/3TC, DTG/RPV and DRV/r/3TC. However, in patients with HBV coinfection, another HBV-active agent must be added to the two-drug regimen used.

3.1 Switching ART regimens

The ART regimens may be changed or switched throughout the course of therapy for a variety of reasons. Reasons for switching include the following:

1. Reduction of cost: Patients who were initially started on TDF/FTC as their pretreatment viral load exceeded 100,000 copies/mL may have their regimens switched to less-expensive ones, such as ABC/3TC, when stable viral suppression is achieved.
2. Reduction of side effects: Similar to the above example, patients can also be switched out of TDF/FTC to minimise or reduce the risks of long-term nephrotoxicity and reduced bone density. Other examples include switching EFV to RPV to reduce neurotoxicity, once virological suppression and immune reconstitution are achieved.
3. Simplification of drug regimen: Switching TDF and 3TC combination to TDF/FTC or ABC/3TC single-tablet combination to reduce pill burden.

The following strategies are for patients without any documented drug resistance or history of treatment failure.

3.2 Switching nucleoside reverse transcriptase inhibitor backbone

Within-class switches from TDF/FTC or zidovudine and 3TC (AZT/3TC) to ABC/3TC are usually well tolerated, provided there is no pre-existing resistance to the switched regimen [Table S5, Supplemental Digital Appendix]. Reasons for switching TDF/FTC to ABC/3TC include nephrotoxicity or bone density loss, while physicians may choose to switch out of AZT/3TC due to lipodystrophy or anaemia. Another benefit of switching out of AZT/3TC is that TDF/FTC and ABC/3TC require only once-daily dosing. Trials have suggested that switching from TDF/FTC to ABC/3TC can maintain virological suppression and even improve serum creatinine and estimated glomerular filtration rate.[84,85] However, the same benefit is not evident for BMD improvement — the OsteoTDF trial showed that while switching from TDF to ABC led to slight improvement in femoral BMD, no differences were found between the two groups.[85] Likewise, physicians may choose to switch from ABC/3TC to TDF/FTC if new cardiovascular risk factors emerge. Switching to TAF/FTC is also another option. Trials show that switching from TDF/FTC to TAF/FTC not only maintained virological suppression, but also led to an improvement in renal function and BMD.[71] Most clinical trials evaluating ART regimen switch (or switch trials) included participants who were virologically suppressed (HIV viral load <50 copies/mL) on their current regimens for at least 48–96 weeks.[71,84,85]

3.3 Switching the third drug

Switching within the same class

Details on switching the third drug are shown in Table S6 [Supplemental Digital Appendix]. The EFV-based regimens are considered alternative first-line regimens in the national recommendations, but as described, they can cause NPSEs. Two main strategies can be employed to address this issue.

1. Reducing the dose of EFV from 600 to 400 mg:
   ENCORE 1 was a non-inferiority trial involving HIV-1–naïve patients who were randomly stratified to either EFV 600 mg or EFV 400 mg combined with TDF/FTC. There was no significant difference in the proportion of participants who had HIV-1 RNA <200 copies/mL at week 48. In addition, study drug-related adverse events were more frequently seen in the 600 mg group as compared to the 400 mg group, with significantly fewer participants with these events stopping treatment in the 400 mg group.[47] Based on these findings, we recommend reducing the dose of EFV from 600 mg to 400 mg as one potential strategy in patients who suffer from NPSEs.
2. Switching EFV to RPV:
   In view of the NPSEs associated with EFV, some investigators have explored switching to a different NNRTI. An open-label, non-inferiority, multicentre study evaluated the efficacy and safety of switching from TDF/FTC/EFV to TDF/FTC/RPV. At week 48, 93.9% of the participants remained suppressed on TDF/FTC/RPV with no treatment-emergent resistance observed. In terms of drug-related adverse events, no participants experienced treatment-emergent adverse events that led to a temporary or permanent discontinuation of the study drug.[86] Likewise, this improved tolerability in terms of NPSEs was also observed in the ECHO and THRIVE trials and in the STar trial.[48,49] Nevirapine is often formulated with AZT and 3TC or stavudine (d4T) and 3TC as a single combination tablet. It is taken as a twice-daily pill and comes with numerous unacceptable adverse effects. It is associated with increased risk of anaemia, neutropenia, nausea and vomiting as compared to a PI-based regimen.[87] In addition, it is associated with increased virological failures and drug mutations, compared to a PI-based regimen.[87] Given the relative superiority of other newer regimens in terms of pill burden, tolerability, barrier to resistance and reduction in cost of newer regimens, the national recommendations strongly suggest that all physicians should switch out patients on NVP-based regimens to other regimens [Table S7, Supplemental Digital Appendix].

Within-class switches can also be applied to other classes of ARV including PI and INSTI, provided there is no treatment-related resistance. For example, ATV/r may be switched to DRV/r, as ATV/r may cause unacceptable jaundice or increase the risk of development of renal stones.

Switching to a different class of ARV

The same principles apply for switching between classes of ARV [Table S6, Supplemental Digital Appendix]. In general, switches can be made as long as there is no treatment-associated resistance, which may include archived resistance as evidenced from previous HIV genotypic resistance testing.

1. Switching PI to NNRTI:
   This strategy has been studied in a randomised, open-label, international, 48-week switch trial, where participants who were virologically suppressed (HIV-1 RNA <50 copies/mL) on a PI-based regimen (containing pharmacologically boosted PI and two NRTIs) were randomised to receive TDF/FTC/RPV or to stay on their current regimen. By week 24, the objective of non-inferiority was met, with 93.7% of the RPV group and 89.9% of the PI group maintaining virological suppression.[88] In extrapolation of the above data and in consideration that lower-dose EFV is associated with reduced adverse events, prescribers may consider switching from ATV/r or DRV/r to EFV 400 mg in individuals without NPSEs, but they cannot be switched to RPV for other reasons (e.g. chronic PPI use, HIV viral load >100,000 copies/mL, CD4 <200 cells/mm^3). Physicians would need to note that NNRTI-based regimens generally have a lower genetic barrier to resistance as compared to PI-based ones.
2. Switching to an INSTI:
   This strategy has been studied in numerous trials. The switch from PI to INSTI was studied in a European trial involving 415 partcipants who were virologically suppressed (HIV-1 RNA <50 copies/mL) for at least 24 weeks. Participants were randomised to switch to a DTG-based regimen versus staying on their PI-based regimen. The trial showed that the proportion of participants remaining virologically suppressed in the DTG-based regimen was not significantly different compared to that in the PI regimen, meeting the criteria for non-inferiority.[89] The switch from NNRTI to INSTI has also been studied in the STRATEGY-NNRTI trial, a randomised, open-label, Phase 3b, non-inferiority trial where participants who were virologically suppressed (HIV-1 RNA <50 copies/mL) on TDF/FTC/NNRTI for at least 6 months were randomised to continue on an NNRTI-based regimen versus TDF/FTC and EVG boosted with cobicistat (EVG/c). At week 48, 93% in the EVG group and 88% in the NNRTI group maintained plasma viral loads below 50 copies/mL, meeting the criteria for non-inferiority.[90]

Switching to a two-drug regimen

There has been increasing evidence that certain two-drug regimens can maintain virological control in patients who initiated therapy and are virologically suppressed for at least 3–6 months on three-drug regimens. There can be multiple reasons for switching to a two-drug regimen. Individuals with CrCl ≤30 mL/min cannot use TDF- or TAF-based regimens (see section 2.7), and presence of chronic kidney diseases puts them at higher risk of myocardial infarction, which also precludes the use of ABC-based regimens.[91] Likewise, individuals with significant cardiovascular risk factors should not be switched to ABC-based regimens. Individuals who are HLA B*57:01 positive also cannot use ABC-based regimens.

However, physicians should note that the following regimens do not cover for HBV infection. In individuals who are HBV coinfected, an additional HBV-active agent, such as entecavir, should be combined with the two-drug regimens for adequate therapy. In addition, physicians should ensure that there are no pre-existing mutations to any of the components of the two-drug regimens before switching, to avoid putting patients on a monotherapy regimen. The following regimens can be used when switching to a two-drug regimen:

1. Switching to DTG/3TC:
   DTG/3TC has been studied in the TANGO trial. A total of 743 participants with HIV infection who had been virologically suppressed (HIV RNA ≤50 copies/mL) for >6 months and had been taking a stable first-line TAF-based regimen were recruited. Participants were randomised into DTG/3TC group or continued on their TAF-based therapy. They had no history of HBV coinfection or evidence of resistance to DTG/3TC. At week 48, DTG/3TC was non-inferior to TAF-based regimen, with 93% of participants in both arms maintaining virological suppression.[92] None of the participants in the DTG/3TC arm met the virological withdrawal criteria, and no emergent resistance was noted.[92] There was a high proportion of participants who withdrew because of adverse effects in the DTG/3TC group, which included anxiety, insomnia, weight increase and fatigue.[92] However, this safety profile is consistent with the safety profile of DTG/3TC in ART-naïve patients, and the overall rates of adverse effects were similar between the two groups.[45,92] In addition, the TAF-based regimen group tolerated their current regimen for a longer period of time and were less likely to withdraw due to adverse effects in comparison to DTG/3TC group.
2. Switching to DTG/RPV:
   Evaluation on DTG/RPV was conducted in the SWORD-1 and SWORD-2 trials. A total of 1024 participants on first-line ART who had been virologically suppressed (HIV RNA <50 copies/mL) for >6 months were randomly assigned to DTG/RPV or who continued on their previous regimen. Of the 511 participants who continued on their previous regimens, 477 were switched over to DTG/RPV at week 52 (late switch group). At week 100, 89% of the early switch group and 93% of the late switch group maintained virological suppression. Drug-related adverse events occurred in 20% of participants in the early switch group and 12% in the late switch group, of which the most common adverse events were headache and nausea.[93]
3. Switching to DRV/r/3TC:
   As mentioned earlier, INSTI-based regimens are superior to PI-based regimens in terms of drug–drug interactions, metabolic side effects and tolerability. In addition, DRV/r/3TC has increased pill burden compared to the earlier two regimens. However, if DTG-based regimens cannot be used, then DRV/r/3TC is a reasonable option. Participants

with HIV RNA <50 copies/mL for >6 months on triple therapy with DRV/r and two NRTIs with no resistance were randomised to continue therapy or switch to DRV/r/3TC. Switching to dual therapy was non-inferior to the triple therapy arm, with 88.9% of participants in the DRV/r/3TC arm and 92.7% of participants in the triple therapy arm maintaining virological suppression at week 48.[94] Four participants in the DRV/r/3TC arm and two in the triple therapy arm withdrew due to protocol-defined virological failure. Serious adverse events and study drug discontinuations were similar between the two arms.[94]

Long-acting ARV

Several international guidelines have included injectable long-acting ARVs in the list of potential switch regimens. The most common regimen that has been studied is intramuscular cabotegravir (CBG) and RPV.[95,96] Both the ATLAS and FLAIR trials, which recruited almost 1200 participants, reported non-inferiority of intramuscular CBG/RPV when compared to oral three-drug standard of care.[95,96] However, CBG/RPV is not licensed in Singapore and is only available on a compassionate access basis. Therefore, this particular strategy is not included in the national recommendations.

3.4 Monitoring parameters in patients with HIV infection

HIV viral load and CD4 cell count monitoring

The viral load is the most important indicator to monitor response to ART and should be monitored at entry into care, initiation and as part of regular follow-up. Several studies have shown that reduction in HIV-1 RNA is associated with reduction in the risk of clinical progression.[97,98] Hence, viral load measurements are important in monitoring adherence to and effectiveness of therapy.

In contrast, CD4 cell count is more useful at the initiation of therapy, when decisions on prophylaxis against OIs have to be made. Subsequently, CD4 cell counts can be repeated every 3–6 months for the first 2 years, after which clinicians may consider to stop monitoring CD4 cell count unless detectable viraemia develops or if the CD4 cell count remains persistently less than 300 cells/mm^3. The initial monitoring helps physicians decide on the ideal timing to stop prophylaxis for OIs. Once the CD4 cell count has recovered and is stable for at least 2 years, CD4 cell count monitoring may be stopped completely. It is important to note that in some patients, especially those who are elderly or who initiate therapy on a lower CD4 cell count, immune recovery may not occur despite virological suppression.[99,100] In these patients, CD4 cell count monitoring can be done every 3–6 months. In cases of immunological recovery, recurrent CD4 cell count monitoring rarely leads to a change in clinical management. In addition, trials have shown that CD4 cell counts rarely fall to <200 cells/mm^3 in settings where there is viral suppression and the CD4 cell count is >300 cells/mm^3.[29,101] Many international guidelines also suggest monitoring can be done annually once patients are stable on ART for between 1 and 2 years and CD4 cell count is >250–350 cells/mm^3.[22-25]

Baseline serologies

Please refer to Tables S8 to S10 [see Supplemental Digital Appendix] for further details on the monitoring labs that should be done for monitoring patients who are initiated and maintained on ART. It is still a common practice locally to check for CMV IgG in all patients newly diagnosed with HIV infection upon entry to care. Measurement of CMV IgG has been removed from both the United States Department of Health and Human Services (DHHS) and International AIDS Society (IAS) guidelines, although the European AIDS Clinical Society (EACS) guidelines still retain it as part of the initial screening panel.[22,24,25] The seroprevalence of CMV-specific antibodies among the adult population is high, ranging between 40% and 100%, with the highest numbers being observed in developing countries throughout Africa and Asia.[102] Given the relatively high seroprevalence of CMV-specific antibodies among adults, there is little utility in using CMV IgG to determine the need for CMVR eye screening. The national recommendations advocate that CMV IgG measurement is not required among all newly diagnosed patients, and that all patients with CD4 count ≤100 cells/mm^3 should have an eye screen before or within 2 weeks of ART initiation to exclude CMVR. This will also have the additional benefit of reducing the cost of treatment to patients locally.

The DHHS and IAS guidelines have also removed *Toxoplasma* antibody testing from their baseline serology panel, while EACS has retained it as part of its initial screening serology panel.[22,24,25] However, in Singapore, up to 53% of newly diagnosed patients have late-stage HIV infection at diagnosis, making toxoplasmosis prophylaxis a crucial part of care for patients who are anti-*Toxoplasma* IgG positive.[103] Hence, the national recommendations recommend that anti-*Toxoplasma* IgG antibody should be checked for all patients at entry to care, so that both ART and appropriate prophylaxis can be started in a timely manner. However, if cost is a concern to patients, physicians can also choose to do anti-*Toxoplasma* antibody only if the CD4 count is <100 cells/mm^3. Likewise, given that 90% of patients with cryptococcal meningitis are seen among patients with CD4 count <100 cells/mm^3, the national recommendations also recommend that physicians consider performing a serum cryptococcal antigen upon entry to care for these individuals.[104]

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Conflicts of interest

There are no conflicts of interest.

Supplemental digital content

Appendix at http://links.lww.com/SGMJ/A113

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APPENDIX

Box 1. Antiretroviral Therapy Choice in ART-naïve Patients

Guideline Notes	
Preferred 1st Line	Should be used as first choice regimen in ART-naïve individuals with no contra-indications to the drugs in this regimen
Alternative 1st Line	Should be used as first choice regimen in ART-naïve individuals with specific contra-indications to the drugs in Preferred 1st Line Regimen OR with specific indications requiring specific antiretroviral drugs (drug-drug interactions e.g., use of chemotherapy) OR where circumstances prevent the use of Preferred 1st Line Regimens (cost considerations) OR as stable switch regimens in specific circumstances
Other	Not mentioned by the various guidelines

Table S1: Tenofovir-based regimens

NRTI backbone	3rd Drug		Singapore	DHHS 2021	IAS 2020	WHO 2021
TFV (TDF or TAF) # / FTC or 3TC	INSTI	DTG	Only if: 1) Hep B co-infected or 2) HLA B*57:01 positive			TDF+3TC/FTC+ DTG
		BIC	BIC is combined with TAF and FTC as a single combination tablet			
		RAL				
	PI	DRV/r				
	NNTI	EFV 400mg OD				
		EFV 600mg OD				
		RPV				

TFV: Tenofovir; TDF: Tenofovir disoproxil fumurate; TAF: Tenofovir alafenamide; FTC: Emtricitabine; 3TC: Lamivudine; NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; INSTI: Integrase strand transfer inhibitor; EFV: Efavirenz; RPV: Rilpivirine; DRV/r: Darunavir/ritonavir; DTG: Dolutegravir; BIC: Bictegravir; RAL: Raltegravir; Hep B: Hepatitis B virus; HLA B5701: Human leukocyte antigen B5701

#TDF to be avoided in patients with CrCl <60 mL/min. TAF to be avoided in patients with CrCl <30 mL/min

Table S2: Abacavir-based regimens

NRTI backbone	3rd Drug		Singapore	DHHS 2021	IAS 2020	WHO 2021
ABC* / 3TC (HLA B*57:01 screening would only be cost-effective in non-Chinese including late-stage Malay and Indian ethnicities)	INSTI	DTG	ABC/3TC/DTG is formulated as a single combination pill			
		RAL				
	PI	DRV/r				
	NNRTI	EFV 400mg OD	Only if: - HIV1 RNA <100,000 copies/ml			
		EFV 600mg OD	Only if: - HIV1 RNA <100,000 copies/ml			
		RPV	Only if: - CD4>200, HIV1 RNA <100,000 copies/ml			

ABC: Abacavir; 3TC: Lamivudine; NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; INSTI: Integrase strand transfer inhibitor; EFV: Efavirenz; RPV: Rilpivirine; DRV/r: Darunavir/ritonavir; DTG: Dolutegravir; BIC: Bictegravir; RAL: Raltegravir
*To be avoided in patients with high cardiovascular risks and patients with HBV co-infection.

Table S3: NRTI-sparing regimens

Regimen	Singapore	DHHS 2021	IAS 2020	WHO 2020
DTG/3TC	Except if HIV RNA > 500,000 copies/mL, HBV co-infection or ART initiated before GRT for NRTI or HBV testing is available			

Table S4: Switching from a three-drug regimen to a two-drug regimen

INITIAL DRUG	REASON TO SWITCH (EXAMPLES)	SWITCH TO	IF	WHEN TO SWITCH
Tenofovir-based regimens (TDF or TAF)	Nephrotoxicity Osteoporosis	DTG/3TC DTG/RPV DRV/r/3TC*	- No resistance to either drug component is present - If patient has HBV-CoI, additional HBV-active agent such as entecavir should be added. *DRV/3TC should only be used if unable to use DTG-based two drug regimens	≥ 6 months stable
ABC-based regimen	Myocardial infarction Significant cardiac risk factors			
TDF: Tenofovir disoproxil fumurate. TAF: Tenofovir alafenamide. ABC: Abacavir; DTG: dolutegravir. 3TC: lamivudine RPV: Rilpivirine. HIV VL: Human Immunodeficiency				

Table S5: Switching NRTI Backbone

INITIAL DRUG	REASON TO SWITCH (EXAMPLES)	SWITCH TO	IF	WHEN TO SWITCH (review guidelines)
TDF/FTC ➔	Documented Side Effects: - Nephropathy - Osteoporosis	ABC/3TC	If cost is a major concern If no significant cardiovascular risk	
	Reduce risk of future side effects with prolonged use	TAF/3TC		≥ 6 months stable
AZT/3TC ➔	Documented Side Effects: - Anaemia - Mitochondrial toxicities	ABC/3TC TDF/FTC		
	Improve Adherence - Reduce dosing frequency			≥ 6 months stable
ABC/3TC	Cardiovascular Risk	TDF or TAF with FTC /3TC		
TDF: Tenofovir disoproxil fumurate; TAF: Tenofovir alafenamide; FTC: Emtricitabine; AZT: Zidovudine3TC: Lamivudine; NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; INSTI: Integrase strand transfer inhibitor; EFV: Efavirenz; RPV: Rilpivirine; DRV/r: Darunavir/ritonavir; DTG: Dolutegravir; BIC: Bictegravir; RAL: Raltegravir				

Table S6: Switching 3rd Drug

INITIAL DRUG	REASON TO SWITCH (EXAMPLES)	SWITCH TO	IF	WHEN TO SWITCH
EFV 600 →	Documented NPSE	EFV 400 (recommended) OR DRV/r (alternative)	HIV VL > 100K OR CD4 < 200	
	Documented NPSE	RPV	HIV VL < 100K OR CD4 >200	
	Improved SE Profile or QoL Enhancement (shift work, etc)	RPV	HIV VL ND AND CD4>200	≥ 6 months stable
	Documented NPSE Improved SE Profile or QoL Enhancement (shift work, etc)	INSTI (DTG)		
EFV 400 →	Documented NPSE	RPV	HIV VL < 100K OR CD4 > 200	
	Improved SE Profile or QoL Enhancement (shift work, etc)	RPV	HIV VL ND AND CD4 > 200	≥ 6 months stable
	Documented NPSE Improved SE Profile or QoL Enhancement	INSTI (DTG)		
ATV/r →	Unacceptable Jaundice OR Kidney or GB stones	EFV 400 (caution → lower barrier to resistance)	No NPSE	
	Unacceptable Jaundice OR Kidney or GB stones	DRV/r	Chronic PPI Use	
	Simplify Regimen	RPV (caution → lower barrier to resistance)	HIV VL ND AND CD4 > 200	≥ 6 months stable
DRV/r →	Simplify Regimen	EFV 400	(HIV VL ND AND CD4 > 200) AND Chronic PPI Use	≥ 6 months stable
	Simplify Regimen	RPV	(HIV VL ND AND CD4 > 200) AND NPSE	
	Simplify Regimen	INSTI (DTG)		
All 3rd Drugs →	Drug-Drug Interactions	INSTI	Care should be taken in specific situations likely to result in significant drug-drug interactions e.g., TB treatment, systemic chemotherapy, anti-coagulation etc. Dose adjustment may be necessary.	

EFV: Efavirenz; ATV/r: Atazanavir/ritonavir; DRV/r: Darunavir/ritonavir; NPSE: Neuropsychiatric side effects; SE: Side effects; QoL: Quality of life; GB: Gallbladder; EFV: Efavirenz; RPV: Rilpivirine; INSTI: Integrase strand transfer inhibitor; DTG: Dolutegravir; HIV VL: Human Immunodeficiency Virus viral load; PPI: Proton pump inhibitor ND: Not detected; TB: Tuberculosis

Table S7: Switching from older single-tablet fixed-dose combinations

INITIAL DRUG	REASON TO SWITCH (EXAMPLES)	SWITCH TO	IF	WHEN TO SWITCH
AZT/3TC/NVP (Z250) ➔ - AZT 250mg / 3TC 150mg / NVP 200mg - Dosed 1 tab 12h	Documented Side Effects: - Anaemia - Mitochondrial toxicities	ABC/3TC/RPV	HLA B*57:01 Negative	
d4T/3TC/NVP (S30/S40) ➔ - d4T 30mg OR 40mg / 3TC 150mg / NVP 200mg - Dosed 1 tab 12h	Improve Adherence - Reduce dosing frequency		HIV VL ND AND CD4 > 200	≥ 6 months stable
AZT: Zidovudine; 3TC: lamivudine; NVP: Nevirapine; d4T: stavudine; ABC: Abacavir; RPV: Rilpivirine; NVP XR: Nevirapine extended release; HIV VL: Human Immunodeficiency Virus viral load; ND: not detected				

Monitoring

Table S8: Monitoring parameters in HIV-infected individuals.

Investigation	Frequency of testing							
	Entry into care	**ART initiation/ change**	**2-12 weeks after ART initiation/ change**	**Every 3-6 months**	**Every 6 months**	**Every 12 months**	**Clinically indicated**	**Treatment failure**
CD4 count	√	√ (only at initiation)		√ During first 2 years of ART or if viremia develops or CD4 <300 cells/mm^3		√ **After 2 years of ART with consistently suppressed viral load** + *Optional once CD4 recovery has occurred, and no clinical decisions need*	√	√

				OR If treatment is delayed		*to be made for OI prophylaxis*		
HIV VL	√	√	√[¥]	√ NB for the first 2 years of treatment	√ NB for stable patients if VL is ND for one year or more and there are no concerns about adherence		√	√
HLA B*57:01		√ If considering ABC (optional) NB Please refer to main text for discussion					NB Note on cost-effectiveness of HLA B*57:01 testing	
Resistance testing	√	√					√ including if ART initiation is delayed	√
Tropism testing		√ If considering CCR5 antagonist					√	√ If considering CCR5 antagonist
Hepatitis A serology (anti HAV total or IgG)	√						√ e.g., post-vaccination	
HIV VL: Human Immunodeficiency Virus viral load; HLA B*57:01: Human leukocyte antigen B5701; ABC: abacavir; CCR5: C-C Chemokine Receptor Type 5; ND: not detected; ART: antiretroviral therapy. Table is adapted from the DHHS guidelines[21]								

Table S9: Monitoring parameters in HIV-infected individuals (2).

Investigation	**Frequency of testing**							
	Entry into care	**ART initiation/ change**	**2-12 weeks after ART initiation/ change**	**Every 3-6 months**	**Every 6 months**	**Every 12 months**	**Clinically Indicated**	**Treatment failure**
Hepatitis B serology (anti HBs, HBsAg, anti HBc total or IgG)	√					√ If non-immune/ non- vaccinated	√	
Hepatitis C antibody test	√					√ If not infected and risk factors present e.g., MSM, PWID	√	
Hepatitis C RNA test	√ If HCV serology positive					√ If previous HCV infection and treated	√	
Syphilis Screening	√				√ If abnormal at last measurement	√ If normal at baseline, annually	√ frequency as per risk behaviour	
Gonorrhoea, chlamydia NAAT	√ from all appropriate sites						√ from all appropriate sites	
Anti-toxoplasmosis IgG	√ If cost is a consideration, to do for patients with CD4 < 100 cells/ mm^3							
Serum cryptococcal antigen	√ *If CD4 < 100< cells mm^3							
FBC	√	√	√ If on AZT	√ If on AZT	√		√	
ALT	√	√	√	√	√		√	
Total Bil			*√ If on ATV/r*	*√ If on ATV/r*	*√ if on ATV/r*		√	
Creatinine	√	√	√	√	√		√	

Anti HBs Ag: Anti Hepatitis B Surface antigen antibody; HBs Ag: Hepatitis B Surface antigen; anti HBc total: Anti Hepatitis B core total antibody; RNA: ribonucleic acid; NAAT: Nucleic acid amplification test; Total Bil: Total bilirubin; HCV: Hepatitis C virus; MSM: Men who have sex with men; PWID: People who inject drugs; AZT: zidovudine; ATV/r: Atazanavir and ritonavir. Table is adapted from the DHHS guidelines [21]

Table S10: Monitoring parameters in HIV-infected individuals (3)

Investigation	**Frequency of testing**							
	Entry into care	**ART initiation/ change**	**2-12 weeks after ART initiation/ change**	**Every 3-6 months**	**Every 6 months**	**Every 12 months**	**Clinically Indicated**	**Treatment failure**
Fasting lipid panel	√	√				√ If normal at last measurement	√ If treatment required: monitoring as clinically indicated	
Fasting glucose and/or HbA1c	√	√				√ If normal at last measurement	√ If treatment required: monitoring as clinically indicated	
Pregnancy test	√ NB if concern for pregnancy	√ NB if concern for pregnancy					√	
Urine glucose and protein	√	√			√		√	
If on TDF regimens								
Serum phosphate		√				√	√	
Other Health Screening								
Smoking	√			√ If smoking	√ If smoking		√	
BP monitoring	√			√ If hypertensive	√ If hypertensive	√ If >120/80mmHg annually	√	
Mood screening	√		√				√	
HAND screening	√						√	
Bone mineral density evaluation							√ TDF-based regimens, age >50, and other risk factors	
TDF: Tenofovir; HAND: HIV-associated neurocognitive disorders; DTG: dolutegravir								