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Recommendations for the use of antiretroviral therapy in adults living with HIV in Singapore

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ABSTRACT

Since the advent of combination antiretroviral therapy (ART), the mortality attributable to HIV infection has been reduced by 80%. Newer antiretroviral agents are highly efficacious, have minimal side effects as compared to older drugs, and can be formulated as combination tablets, which reduces patients' pill burden. Despite these advances, 680,000 people died of AIDS-related illnesses worldwide in 2020. The National ART and Monitoring Recommendations by the National HIV Programme are 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. 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 ending of HIV in our lifetime.

Keywords: ART, HIV, recommendations

What's new in the Recommendation:

1. Cost considerations
   16 ARVs have been included in the subsidized drug list as of 1 September 2020. This change greatly reduces cost of ART for patients, including DTG-based regimens.

2. Selection of ART
   - DTG-based and BIC-based regimens are now recommended as first line regimens in view of the numerous advantages they have over NNRTI-based regimens. This is due to evidence of increasing NNRTI resistance and the inclusion of DTG in the subsidized drug list, making INSTI-based regimens increasingly affordable (Tables I, II and III)
   - The NRTI-sparing regimen DTG/3TC has also been included as a first line regimen, with caveats (Table III).
   - NNRTI-based regimens have now been moved to alternative first line regimens (Table I and II)
   - ATV/r has been removed from the alternative first line regimen under PI-based regimen

3. Switching ART in the setting of virologic suppression
   - Two-drug regimens have been added as part of the strategy for switching ART regimens (Table VII)
   - Increased emphasis has been placed on the switching of NVP-based regimens to other regimens (either within class or cross class switch)

4. Monitoring
   - CMV 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.

INTRODUCTION TO HIV AND ART

The treatment of Human Immunodeficiency Virus (HIV) infection has come a long way from the time of its initial description as the cause of the Acquired Immunodeficiency Syndrome (AIDS) in 1981, transforming a formerly fatal illness into a chronic although not yet curable disease. Since the advent of combination antiretroviral therapy (ART), the mortality attributable to HIV infection has been reduced by 80%.[1,2] Newer antiretroviral agents (ARV) are highly efficacious, have minimal side effects as compared to older drugs, and can be formulated as single-table combination regimens which reduce pill burden experienced by patients.

In addition to improving the mortality and morbidity of individuals living with HIV infection, treatment is also crucial in 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 which 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 HPTN 052 trial, wherein 1763 serodiscordant couples were enrolled from 9 countries and randomised to receive either early or delayed ART. The couples enrolled consisted of heterosexual men and women, men who have sex with men (MSM) and women who have sex with women (WSW). 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 (CYFU). There were no phylogenetically linked partner transmissions.[4] In the Opposites Attract study, 343 serodiscordant MSM couples were enrolled. Following 16800

acts of condomless penetrative sexual intercourse observed in the study, no phylogenetically linked HIV transmission were observed.[5]

Despite these advances, 680 000 people died of AIDS-related illnesses worldwide 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 fewer than 500 000 new HIV infections globally by 2020. Since then, the number of new HIV diagnoses have 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 (UNAIDS) 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 have HIV infection are aware of their serostatus; 91% of these are receiving treatment and 91% of those on ART have achieved durable viral suppression.[9] While these findings are promising, more can be done to increase HIV testing rates, and we should continue efforts to encourage people living with HIV to initiate and remain on therapy.

The National ART and Monitoring Recommendations by the National HIV Programme are 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 document.

SECTION 1: INTRODUCTION

Key Points

ART should be started for all individuals within 2 weeks of presentation to care, barring some exceptions:

(1) Tuberculosis
We recommend that ART should be started within 2 weeks of TB treatment initiation for patients with CD4 count less than 50 cells/mm^3, but started within 2-8 weeks of TB treatment initiation if the CD4 count is 50 cells/mm^{3}and above.

(2) CMV retinitis
The optimal timing of ART initiation should be individualized. Joint management by an HIV physician and an ophthalmologist with expertise in managing CMV retinitis
is required.

(3) CNS opportunistic infections
We recommend that ART should be delayed in patients with CNS OIs until specific treatment for these OIs has been initiated, and clinical improvement observed.

When to start ART

ART 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 an 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 only started once 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 and 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 specific OIs as below.

Tuberculosis (TB)

In general, multiple trials have shown that ART should not be delayed until completion of TB treatment. Early initiation of ART in patients with TB has been shown to be associated with improved mortality and reduced risk of opportunistic infections. 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 as compared to the delayed ART group, with a higher risk of clinically apparent immune reconstitution in the early ART group.[17]

CMV retinitis (CMVR)

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

Central nervous system (CNS) OIs

Early initiation of ART in patients with cryptococcal meningitis or tuberculosis meningitis may result in serious complications due to IRIS, and some trials demonstrate 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 CNS tuberculosis, 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

Key Points

(1) The inclusion of most ART into the national subsidised drug list from 1 September 2020 has made the treatment of HIV increasingly more affordable.

(2) DTG and BIC-based regimens are the preferred first line regimens (Table I, II, III). These include:
   (a) **TDF or TAF / FTC or 3TC based regimens**: combined with DTG. BIC is currently only available as a combination tablet with TAF/FTC (Biktarvy®)
   (b) **ABC/3TC based regimens**: A combination tablet consisting of ABC, 3TC and DTG is available (Triumeq®)
   (c) **NRTI-sparing regimens**: DTG/3TC
   (d) RAL-based regimens are no longer recommended as first line regimens.

(3) NNRTI- and DRV/r-based regimens can be considered as alternative first line regimens if INSTI-based regimens cannot be used.

(4) Tenofovir-containing regimens:
   (a) TDF-containing regimens should be avoided in individuals whose CrCl is below 60mL/min.
   (b) TAF-containing regimens should be avoided in individuals with CrCl < 30mL/min.

(5) Abacavir-containing regimens
   (a) HLA B*57:01 testing prior to 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 VII).
   (b) ABC should be avoided in patients with high cardiovascular risk, or in those with a documented history of ischemic heart disease.
   (c) ABC should be avoided in individuals with a pre-treatment 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-HBV co-infection. If ABC/3TC must be used in these individuals, an additional HBV-active agent such as entecavir should be added.

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 I: 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 II: 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 III: 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			

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 co-infections or other co-morbid conditions. Likewise, the general principles for ART selection in the local context are based on the above principles. In addition, cost-effectiveness is also an important consideration to ensure sustained universal access to ART in Singapore.

Cost considerations

Singapore uses a co-payment model in ART financing, with some of the cost of treatment being borne by the patient. Since 1 September 2020, majority of the ART has 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 percent to 75 percent worth of subsidies, depending on patient's means testing outcomes.[26, 27]

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, bictegravir (BIC) is not included in the subsidised drug list. A study done in the United States demonstrated 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 minimize 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 was useful in the first 48 weeks of treatment, patients who have otherwise responded with HIV-

1 RNA less than 50 copies/mL and rise in CD4 count equal to or above 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 the testing for the HLA B*57:01 allele. While international guidelines advise that HLA B*57:01 testing should be performed prior to using abacavir, a study done in Singapore showed that HLA-B*5701 testing is only cost effective in Malay and Indian patients with late-stage HIV infection (please see section on Abacavir under Nucleoside Reverse Transcriptase Inhibitors for further elaboration).[30] The decision to perform this test prior to initiation of ABC-containing regimens should hence be considered on a patient-to-patient basis.

Integrase strand transfer inhibitors (INSTI) regimens

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 with non-nucleoside reverse transcriptase inhibitors (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 WHO has also recommended DTG-based regimens as first line regimen in adults and children.[31] Singapore's transmitted drug resistance data was provided to the NHIVP by the National Public Health Laboratory (NPHL) during the NHIVP 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 subsidized drug list has made INSTI- based regimens increasingly affordable.[27]

Hence, in view of the above advantages and drug resistance trends, the national recommendations also recommend DTG- and BIC- based regimens as first line regimens. Raltegravir (RAL)-based regimens are not listed as first line as RAL has a lower genetic barrier to resistance as compared to DTG and BIC.[32,33] Elvitegravir (EVG), which is usually co-formulated with cobicistat, has many significant drug interactions which limits its ease of use, and is not widely available in Singapore, and therefore is not included in the national recommendations.

Compared to efavirenz (EFV)-based regimens, DTG has been shown to result in higher rates of virologic suppression, and is better tolerated with fewer discontinuations due to side-effects. The SINGLE trial, a randomised double-blind phase 3 study comparing abacavir (ABC)/lamivudine (3TC)/DTG versus tenofovir disoproxil fumurate (TDF)/emtricitabine (FTC)/EFV once daily in treatment-naïve patients with HIV-1 infection, showed that a higher proportion of patients achieved a HIV viral load of less than 50 copies/ml when receiving ABC/3TC/DTG when compared to TDF/FTC/EFV in week 144, meeting 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 although the incidence of insomnia was higher in the group receiving DTG.[34] There were no drug resistance mutations detected in the ABC/3TC/DTG group, while one TDF-associated mutation and four EFV-associated mutations were detected in the participants with virologic failure in the TDF/FTC/EFV group.[34]

Likewise, in comparison to protease inhibitors (PI), DTG was associated with fewer adverse events and increased tolerability. This was demonstrated in the FLAMINGO trial, which was a 96-week, multi-centre, open-label, phase 3b non-inferiority trial where treatment-naïve patients with HIV-1 infection were randomly assigned to receive DTG 50mg once daily

or darunavir (DRV) 800mg plus ritonavir 100mg (DRV/r) once daily in combination with either TDF/FTC or ABC/3TC. 13 participants in the DRV/r group discontinued because of adverse events in comparison to 6 participants in the DTG group. Fewer adverse events were observed in the DTG group as 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 effects specific to INSTI-based regimens. Sax et al 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.[36] Although DTG has significantly less neuropsychiatric side effects (NPSE) compared to EFV-based regimen, there are still significant symptoms of insomnia and sleep disorders being reported.[34,37] These adverse effects are not absolute indications to cease DTG-based therapy, and physicians should discuss with patients on 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 (NTD) 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. There were no neural tube defects noted in either the DTG exposed group and the EFV or RAL group.[40] In view of this, the World Health Organisation released a statement in July 2019 recommending the use of DTG as preferred first-line and second-line treatment for all HIV-infected individuals, including pregnant women and those 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 that DTG-based regimens can be used as part of the first-line regimen for all HIV-infected individuals, including women of childbearing potential (Table I, II and III).

BIC, which is combined with Tenofovir alafenamide (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. BIC has been recently approved by the U.S 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 three 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 randomised controlled trial comparing TAF/FTC/BIC (co-formulated as a single tablet) versus ABC/3TC/DTG (co-formulated as a single tablet) for 144 weeks. At the end of 48 weeks, the BIC group was non-inferior in terms of virological suppression to the DTG group, with no emergent drug resistance.[42] In addition, BIC was well tolerated with better gastrointestinal tolerability as 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 abacavir 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' co-infection 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] BIC-based regimens are also associated with weight gain.[36] In a pooled analysis of eight randomised controlled trials in ART-naïve individuals, the weight gain between DTG-and BIC- based regimens were similar.[36] There is also limited data concerning the use of BIC around the time of conception and pregnancy, hence it should not be used in individuals who are pregnant or planning for pregnancy until more data is available. In view of the above 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 co-infection) and in individuals for whom cost is not a significant consideration.

Nucleoside reverse transcriptase inhibitors (NRTI)-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.

DTG/3TC has been studied in the GEMINI-I and GEMINI-II trials. 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 virologic 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. Virologic nonresponse was also uncommon, occurring in 3.1% of the participants in DTG/3TC group and 2% of participants in 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 first line regimen for individuals with HIV RNA < 500,000 copies/ml and no evidence of HBV-co infection. 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 yet widely available in Singapore. Physicians should note that individuals on this regimen will have a higher pill burden compared to individuals on other DTG-based regimens.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) based regimens

EFV has a long track record of use with high potency. It can also be used for patients who require anti-tuberculous treatment as dose adjustment of rifampicin and EFV are not required, although the 400mg dose of EFV is not recommended in this clinical context. However, it is associated with significant neuropsychiatric side effects (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, or 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 cost of NNRTI-based regimens were significantly lower than 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 as compared to INSTI-based regimens, NNRTI-based regimens are now moved to alternative first line therapy in the national recommendations.

EFV remains a highly potent ARV, despite recent RCTs demonstrating the superiority of DTG in achieving virologic suppression. EFV is non-inferior to protease inhibitors like boosted atazanavir (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 400mg instead of 600mg. This dosing has been showed in the ENCORE 1 trial to be non-inferior in terms of virologic suppression to the standard dosing of 600mg, with significantly fewer adverse events observed in the 400mg dosing group as compared to the 600mg 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 (Table I and II). In patients with significant NPSE on EFV-based regimens the dose of EFV can be reduced to 400mg instead of 600mg.

Rilpivirine (RPV) has also been recommended as an alternative regimen if INSTI regimens cannot be used.[22,23] RPV-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 pre-treatment HIV viral load exceeds 100,000 copies/mL and pre-treatment CD4 count is <200 cells/mm^3. This is seen in the ECHO and THRIVE trial as well as the STar trial, where it is found to be non-inferior to EFV only if pre-treatment HIV viral load was less than 100,000 copies/ml.[48,49] In addition, for optimal absorption, it needs to be taken with meals comprising at least 390 calories, and co-administration with proton-pump inhibitors must be avoided. RPV demonstrated improved tolerability compared to 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 pre-treatment HIV viral load is < 100,000 copies/mL and CD4 count is >200 cells/ mm^3 in individuals who cannot use INSTI- based regimens (Table I and II).

Doravirine (DOR) has been included in many international recommendations as 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 group. At 96 weeks, 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. NPSEs and rash were more common in EFV arm.[51] DOR has also been compared against DRV/r in the DRIVE-FORWARD trial, where 769 ART-naïve individuals were randomised to receive DOR versus DRV/r combine 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 virologic 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] DOR has not yet been compared with INSTI. However, DOR is currently still not widely unavailable in Singapore and hence is not included in the recommendations.

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 on 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 first line regimen to alternative first line regimen.

As described above, 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. RPV cannot be used if the pre-treatment HIV viral load is more than 100,000 copies/ml, as it is associated with more virologic 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 co-administered with proton pump inhibitors (PPI).

The combination of TDF/FTC (or 3TC)/EFV has a low genetic barrier to resistance as all three component ARVs only require a single base-pair substitution each to result in drug resistance (K65R for TDF, M184V for FTC or 3TC, and K103N for EFV respectively). In patients who are non-adherent to this regimen, virologic 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 (ETR).[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 than EFV-based regimens.[57] Although DTG and EFV 400mg 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 were 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. EFV 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 virologic efficacy has also been demonstrated in RPV if the pre-treatment HIV viral load is less than 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 NPSE such as insomnia and sleep disorders.[36,37] EFV- or RPV- based regimens are less costly than DTG-based regimens. As Singapore uses a co-payment 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 above points, we recommend NNRTI-based regimens as 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 (Table I and II).

Protease inhibitor (PI) 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 regimens listed above.[22-25] As they are potent hepatic CYP 3A4 enzyme inhibitors, they are associated with significant drug-drug interactions as compared to INSTI and NNRTI-based regimens. In addition, they are also 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 (co-administered with ritonavir [RTV or /r] as a pharmacologic booster). In a trial by Sax et al, patients who were on ABC/3TC and either ATV/r or EFV, the time to virologic failure was significantly shorter with ATV/r as compared to 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 pre-treatment HIV viral load is < 100,000 copies/mL.[59]

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 virologic efficacy was similar with all three agents, DRV/r demonstrated improved tolerability as compared to ATV/r. Overall, however, RAL was superior to both PIs in terms of a composite endpoint of virologic efficacy and tolerability.[60] This was also seen in the FLAMINGO trial, where a DTG-based regimen was superior to DRV/r-based regimen when in terms of both virologic efficacy and tolerability at 48 weeks.[61] Hence in consideration of the above points, PI- based regimens should be used as an alternative first line regimen if an NNRTI-based or INSTI-based

first line regimen cannot be used (Table I and II). If a PI-based regimen is used, DRV/r is recommended over all other PI.

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

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 instead to save cost. This combination is not available as a single tablet combination.

Tenofovir: Tenofovir disoproxil fumarate (TDF) and Tenofovir alafenamide (TAF)

The two main concerns with TDF use are the risk of renal and bone toxicities. TDF use has been associated with new-onset or worsening renal impairment.[62] This risk is noticeably higher among females, and patients with lower body weight, pre-existing renal impairment, and the use of a protease inhibitor-based regimen.[63,64] In addition, TDF has been associated with a decline in BMD, especially when compared to ABC.[65] There have also been cases of osteomalacia 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 below 60mL/min.[22-25] Likewise, the national recommendations also agree that TDF-containing regimens should be avoided in individuals whose CrCl is below 60mL/min^2.

TAF 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

randomized into TAF or TDF combined with EVG. At 144 weeks, TAF had less impact than TDF on bone mineral density and renal biomarkers.[68] No participants had to discontinue TAF due to renal adverse effects as compared to TDF.[68] This observation was also seen in other trials.[69,70] The same benefits were also noted when switching from TDF to TAF- based regimen. In a randomized, multicentre, open label study switching patients from TDF- based regimens to TAF-based regimens, improved bone mineral density and renal function were noted among patients who were switched to TAF-based regimens.[71] Some studies reported significant weight gain among individuals on TAF-based regimens compared to TDF-based regimens, but the clinical significance of this finding is still unclear.[36,72] As there is limited data on the use of TAF in patients with CrCl < 30mL/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 < 30mL/min. Despite the advantages of TAF 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 are still retained as first line regimen for individuals who require tenofovir use but have significant cost concerns (Tables I and II).

Abacavir (ABC)

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 done 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 population was 0.26%, 2.44% and 15.10% respectively.[30] In the study, late-stage HIV infection was defined

as CD4 count < 200 cells/mm^3. Genotyping prior to ABC use was found not 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 ethnicity.[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 prior to the use of ABC only for non-Chinese patients, including lndian and Malay patients with late-stage HIV infection (CD4 < 200 cells/mm^3) (Table VI), and that the decision to test before initiation treatment be made on a patient-to-patient basis.

An association between ABC use and myocardial infarction (MI) was first noted in the D:A:D study, where exposure to ABC was associated with an increased risk of MI in the first 6 months after initiation of the drug.[76,77] There were other trials that also replicated this finding.[78,79] However, there are also studies that did not show this association, including a United States FDA meta-analysis of 26 trials that evaluated ABC.[80,81] As such, no clear conclusion can be made about the association with ABC and MI. 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 through the use of cardiovascular disease risk calculators, such as the Framingham general cardiovascular Risk Score (FRS).[82] However, it is important to note that not all risk calculators have been validated in HIV-infected populations. We also recommend that ABC should be avoided in patients with high cardiovascular risk, or in those with a documented history of ischemic heart disease.

As mentioned in the section on NNRTI and PI, ABC has reduced virologic efficacy compared to TDF if the pre-treatment viral load is ≥100,000 copies/ml. In the ACTG 5202

study, a randomised control trial 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 pre-treatment viral load ≥100,000 copies/ml, the time to virologic 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 a HIV viral load of less than 50 copies/ml per millimetre when receiving ABC/3TC/DTG when compared to TDF/FTC/EFV in week 144.[34] ABC also cannot treat HBV infection and the use of lamivudine alone in HIV-HBV co-infection has been associated with lamivudine resistance in HBV.[83] ABC should be avoided in individuals with a pre-treatment 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-HBV co-infection. If ABC/3TC must be used in these individuals, an additional HBV-active agent such as entecavir should be added.

Comparing ABC/3TC versus TDF/FTC

TDF/FTC and ABC/3TC have been compared in the ACTG 5202 trial, a randomised controlled trial of > 1800 participants where the efficacy and safety of TDF/FTC and ABC/3TC with either EFV or ATV/r was compared. In patients with baseline HIV viral load > 100,000 copies/mL, there was a significantly shorter time to virologic 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 VL > 100,000 copies/mL, the combination of ABC/3TC with EFV should be avoided.

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

Key Points

1) The national recommendations recommend that patients should be virologically suppressed for at least 6 months prior to considering switching.

2) The follow strategies can be employed when switching ART regimens in the setting of virologic suppression (table IV-VII):

   (A) Switching NRTI backbone;
   (B) Switching the 3rd drug
   (C) Switching from older single- tablet fixed dose combinations to combination tablet;
   (D) Switching from a three-drug regimen 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 VII). Possible combinations that can be use 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.

Table IV: 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 V: 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 VI: 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				

Table VII: 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				

Switching antiretroviral regimens

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

(1) Reduction of cost: Patients initially started on TDF/FTC as pre-treatment viral load exceeds 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 example above, patients can also be switched out of TDF/FTC to minimise or reduce risk of long-term nephrotoxicity and reduced bone density. Other examples include switching EFV to RPV once virologic suppression and immune reconstitution are achieved to reduce neurotoxicity.

(3) Simplification of drug regimen: Switching TDF and 3TC combination to TDF/FTC or ABC/3TC single tablet combination to reduce pill burden.

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

Switching NRTI backbone (Refer to Table IV)

Within class switches from TDF/FTC or zidovudine and lamivudine (AZT/3TC) to ABC/3TC are usually well tolerated provided there are no pre-existing resistance to the switched regimen. 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 only require once daily dosing. Trials have suggested that switching from TDF/FTC to ABC/3TC can maintain virological suppression and even improve serum creatinine and eGFR.[84, 85] However, the same benefit is not as evident for bone mineral density improvement- the OsteoTDF trial showed that while switching from TDF to ABC led to slight improvement in femoral bone

mineral density, no differences were detected 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 maintained virologic suppression, but also led to an improvement in renal function and bone mineral density.[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]

Switching the third drug (Table V)

Switching within the same class

EFV-based regimens are considered alternate first line regimens in the national recommendations, but as described above, can cause neuropsychiatric side effects. Two main strategies can be employed to address this issue.

- Reducing the dose of EFV from 600mg to 400mg

  ENCORE 1 was a non-inferiority trial involving HIV-1 naïve patients who were randomly stratified to either EFV 600mg or EFV 400mg 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 600mg group as compared to the 400mg group, with significantly fewer participants with these events stopping treatment in the 400mg group.[47] Based on these findings, we recommend reducing the dose of EFV from 600mg to 400mg as one potential strategy in patients who suffer from neuropsychiatric side effects.

- Switching EFV to RPV

  In view of the neuropsychiatric side effects 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 neuropsychiatric side effects was also observed in the ECHO and THRIVE trial as well as the STar trial.[48,49]

NVP 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, neutropaenia, nausea, vomiting compared to PI-based regimen.[87] In addition, it is also associated with increased virologic failures and drug mutations compared to a PI 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 recommend that all physicians should switch out patients on NVP-based regimens to other regimens (Table VI).

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 (Refer to Table V)

The same principles apply for switching between classes of ARV. 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.

- 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 NRTI) 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 virologic suppression.[88] In extrapolation of the above data and in consideration that lower dose EFV is associated with reduced adverse events, prescribers may considerswitching from ATV/r or DRV/r to EFV 400mg in individuals without neuropsychiatric side effects, but cannot be switched to RPV for other reasons (e.g. chronic proton-pump inhibitor use, HIV VL > 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 a PI-based ones.

- 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 as compared to the PI regimen, meeting 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 continuing on an NNRTI-based regimen versus TDF/FTC and Elvitegravir boosted with cobicistat (EVG/c). At week 48, 93% in the EVG

group and 88% of the NNRTI group maintained plasma viral loads below 50 copies/mL, meeting criteria for non-inferiority.[90]

Switching to a two drug regimen

There has been increasing evidence that certain two drug regimens can maintain virologic 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 ≤ 30ml/min cannot use TDF- or TAF- based regimens (refer to section on NRTI), and presence of chronic kidney diseases put them at higher risk myocardial infarction which also precludes the use of ABC- based regimens.[91] Likewise, individuals at significant cardiovascular risk factors should be not 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 co-infected, 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 prior to switch to avoid putting patients on a monotherapy regimen. The following regimens can be used when switching to a two drug regimen:

- Switching to DTG/3TC

  DTG/3TC has been studied in the TANGO trial. 743 participants with HIV infection who have been virologically suppressed (HIV RNA ≤ 50 copies/ml) for > 6 months taking a stable first line TAF-based regimen were recruited. Participants were randomized into DTG/3TC group or continued on their TAF-based therapy. They had no history of HBV co-infection 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 virologic

suppression.[92] None of the participants in DTG/3TC arm met virologic 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 was similar between the two groups.[45,92] In addition, the TAF-based regimen group has 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.

- Switching to DTG/RPV

  DTG/RPV was studied on the SWORD-1 and SWORD-2 studies. 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 continued on their previous regimen. Of the 511 participants 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 maintain virologic suppression. Drug related adverse events occurred in 20% of participants in the early switch group and 12% of the late switch group, of which the most commonly adverse events are headache and nausea.[93]

- Switching to DRV/r/3TC

  As mentioned earlier, INSTI-based regimens are superior to PI-based regimen 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 2 NRTI with no resistance were randomized 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 virologic suppression at week 48.[94] Four participants in the DRV/r/3TC arm and 2 in the triple therapy arm withdrew due to protocol defined virologic 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 ARV 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, demonstrated that 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.

Monitoring

Table VIII: 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 OR If treatment is delayed		√ **After 2 years of ART with consistently suppressed viral load** + *Optional once CD4 recovery has occurred, and no clinical decisions need 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 IX: 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 X: 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								

Some points to note on 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 was associated with reduction in the risk of clinical progression.[97,98] Viral load measurements are thus important in monitoring adherence to, and effectiveness of therapy.

In contrast, CD4 cell count is more useful at initiation of therapy, when decisions on prophylaxis against opportunistic infections 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 opportunistic infections. Once 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 virologic suppression.[99,100] In these patients, CD4 cell count monitoring can be done every 3-6 monthly. In cases of immunologic 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 less than 200 cells/mm^3 in the setting of viral suppression and CD4 cell count more than 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 to 2 years and CD4 cell count is more than 250- 350 cells/mm^3.[22-25]

Baseline serologies

It is still a common practice locally to check for CMV IgG in all patients newly diagnosed with HIV infection upon entry to care. CMV IgG measurement has been removed from both the DHHS and IAS guidelines, although the 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 to 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 CMV retinitis eye screening. The national recommendations recommend that CMV IgG measurement is not required among all newly diagnosed patient and all patients with CD4 count ≤ 100 cells/mm^3 should have an eye screen prior to or within 2 weeks of ART initiation to exclude CMV retinitis. This will also have at the additional benefit of reducing the cost of treatment to patients locally.

DHHS and IAS guidelines have also removed *Toxoplasma* antibody testing from their baseline serology panel, while EACS has retained it as part of their 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 cryptococcal meningoencephalitis are seen among patients with AIDS and CD4 count is < 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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