National HIV Programme: Recommendations for the Use of Antiretroviral Therapy (ART) in Adults Living in Singapore

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List of abbreviations

Abbreviations listed are arranged in alphabetical order

Abbreviations	Definition
3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral therapy
ARV	Antiretroviral agents
ATV/r	Atazanavir boosted with ritonavir
AZT	Zidovudine
BIC	Bictegravir
CAB	Cabotegravir
CMV	Cytomegalovirus
CMVR	CMV retinitis
CNS	Central nervous system
CrCl	Creatinine clearance
d4T	Stavudine
DOR	Doravirine
DRV/r	Darunavir boosted with ritonavir
DTG	Dolutegravir
EFV	Efavirenz
EVG/c	Elvitegravir boosted with cobicistat
FDA	U.S Food and Drug Administration
FRS	Framingham general cardiovascular Risk Score
FTC	Emtricitabine
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
INSTI	Integrase strand transfer inhibitors
IRIS	Immune reconstitution inflammatory syndrome
LA	Long-acting
MSM	Men who have sex with men
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NPSE	Neuropsychiatric side effects
NPV	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitors
NTD	Neural-tube defects
OI	Opportunistic infections
PI	Protease inhibitors
PrEP	Pre-Exposure Prophylaxis
RAL	Raltegravir
RCT	Randomised controlled trials
RNA	Ribonucleic acid
RPV	Rilpivirine
RTV	Ritonavir
TAF	Tenofovir alafenamide

Abbreviations	Definition
TasP	Treatment as Prevention
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
WSW	Women who have sex with women
XTC	3TC or FTC

What is new in the recommendations?

1. Selection of ART
   - TDF/TAF- based regimen with 3TC/FTC combined with DRV-r has been included as a first line regimen for individuals who acquire HIV while using CAB-LA as PrEP (Table IV)
   - DTG/3TC is now available in Singapore as a single tablet formulation.
   - RAL has been removed as an option under alternative regimens (Table I, II)

2. Switching ART in the setting of virologic suppression
   - IM CAB/RPV has been included as an option for switching ART in individuals who are virologically suppressed.
   - When switching to a two-drug regimen, individuals who are virologically suppressed with archived 3TC- associated mutations and or/prior virological failures can still consider switching to DTG/3TC as a strategy.
   - A "special consideration" segment has been added to this section that discusses switching to TAF/TDF/XTC with either BIC or DTG in individuals who have pre-existing NRTI resistance.

3. Monitoring
   - An addendum has been added to Table IX indicating that HIV viral load monitoring should be done 4 to 8 weeks after switching to IM CAB/RPV.

4. New section
   - A new section on antenatal and perinatal care and monitoring of women living with HIV and their infants has been added to the recommendations.

Abstract:

Since the advent of combination antiretroviral therapy (ART), the mortality attributable to HIV infection has been reduced by 80%. 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 with a reduced pill burden. Despite these advances, 650 000 people died of AIDS-related illnesses worldwide in 2021. As of end 2022, a total of 9331 Singapore residents have been diagnosed with HIV infection, of whom 2362 have died. The 'Recommendations for the Use of Antiretroviral Therapy (ART) in Adults Living with HIV in Singapore by the National HIV Programme' was developed to guide physicians on the prescribing of ART. The national recommendations are based on international guidelines, which had previously been applied in Singapore prima facie, and are now tailored to the local context to take into account unique domestic considerations. It is hoped that with the publication of the national recommendations, the care of people living with HIV can be improved, bringing us closer to the goal of ending HIV in our lifetimes.

Keywords: HIV, ART, Recommendations

CONTENTS

Introduction to HIV and ART

The history of the treatment of Human Immunodeficiency Virus (HIV) infection has come a long way from the time of its initial description as the cause of Acquired Immunodeficiency Syndrome (AIDS) in 1981, transforming a formerly fatal disease 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-tablet 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 do not pose the risk of transmitting HIV. The first of these trials was the HIV Prevention Trials Network (HPTN) 052 trial, where 1,763 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 initiation of 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 was observed.[5]

Despite these advances, 650,000 people died of AIDS-related illnesses worldwide in 2021.[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 95-95-95 targets by 2025, where 95% of all people living with HIV will know their diagnosis; 95% of all people diagnosed with HIV infection will receive ART; and 95% of all people receiving ART will achieve durable viral suppression.[8] As of 2020, 83% of people in Singapore who have HIV infection are aware of their serostatus; 94% of these are receiving treatment and 95% 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.

Recognising that the international guidelines may not take into consideration the unique milieu of HIV care in Singapore, the ART Recommendations Workgroup, convened by the National HIV Programme (NHVIP), met to develop guidance for physicians on how to prescribe ART for individuals living with HIV in Singapore. The Workgroup consisted of clinicians and researchers with expertise in HIV, as well as representatives of community-based organisations involved in Singapore's HIV response and adopted a consensus decision making process. The National ART and Monitoring Recommendations are created to:

a) Guide physicians on the prescribing of ART based on the unique needs and situation of patients in Singapore.
b) Guide physicians on the monitoring of people living with HIV on ART based on the unique needs and situation of patients in Singapore.
c) Align disparate practices between HIV physicians in Singapore.

These recommendations are based on international guidelines by organisations such as the Department of Health and Human Services (DHHS), European AIDS Clinical Society (EACS), International AIDS Society (IAS) and World Health Organisation (WHO), which were tailored to the local context and unique domestic considerations[10-13]. It is hoped that with the publication of these recommendations, the care of people living with HIV in Singapore 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 several exceptions:

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

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

(3) CNS opportunistic infections (OIs)
We recommend that ART 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).[14, 15] 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.[15-18] 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.[19] However, ART should be delayed in the settings of specific OIs mentioned 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 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.[20] This is likewise supported by the CAMELIA and ACTG A5221 trials.[21, 22] 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.[21]

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.[23, 24] 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.[25]

Section 2: ART Selection

Key Points

For individuals who do not have a history of using CAB-LA as PrEP, the following regimens are recommended:

(1) 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

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

(3) RAL- based regimen has been removed as an alternative first line regimen.

For individuals who have a history of using CAB-LA as PrEP, the following regimen should be used if treatment is started prior to the results of HIV genotypic resistance testing.

(4) **Boosted DRV-r combined with TDF or TAF/ FTC or 3TC based regimen-** pending results of genotypic resistance testing (Table IV)

(5) 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.

(6) Abacavir-containing regimens:
   (a) HLA B*57:01 testing prior to the use of ABC is only necessary for patients not ethnically Chinese, including Indian and Malay patients with late-stage HIV infection (CD4 < 200 cells/mm^3) (Table II), though this decision should be individualised to the patient.
   (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

Individuals who do not have a history of using CAB-LA as PrEP prior to acquiring HIV:

Table I: Tenofovir-based regimens

NRTI backbone	3rd Drug		Singapore	DHHS 2022	IAS 2022	EACS 2022	WHO 2021
TFV (TDF or TAF) # PLUS FTC or 3TC	INSTI	DTG	Only if: 1) Hepatitis 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				
	PI	DRV/r					
	NNTI	EFV 400mg OD					
		EFV 600mg OD					
		RPV					

TFV: Tenofovir; TDF: Tenofovir disoproxil fumarate; TAF: Tenofovir alafenamide; FTC: Emtricitabine; EACS: European AIDS Clinical Society; 3TC: Lamivudine; NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; IAS: International AIDS Society; INSTI: Integrase strand transfer inhibitor; EFV: Efavirenz; RPV: Rilpivirine; DRV/r: Darunavir/ritonavir; DTG: Dolutegravir; DHHS: Department of Health and Human Services; BIC: Bictegravir; RAL: Raltegravir; Hep B: Hepatitis B virus; HLA B5701: Human leukocyte antigen B5701; WHO: World Health Organisation

#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 2022	IAS 2022	EACS 2022	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 tablet.				
	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; IAS: International AIDS Society; INSTI: Integrase strand transfer inhibitor; EACS: European AIDS Clinical Society; EFV: Efavirenz; RPV: Rilpivirine; DRV/r: Darunavir/ritonavir; DTG: Dolutegravir; DHHS: Department of Health and Human Services; BIC: Bictegravir; RAL: Raltegravir; WHO: World Health Organisation

*To be avoided in patients with high cardiovascular risks and patients with HBV co-infection.

Table III: NRTI-sparing regimens

Regimen	Singapore	DHHS 2022	IAS 2022	EACS 2022	WHO 2021
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				

DHHS: Department of Health and Human Services; IAS: International AIDS Society; EACS: European AIDS Clinical Society; WHO: World Health Organisation

<u>Individuals who have a history of using CAB-LA as PrEP:</u>

Table IV: Regimen for individuals who have a history of using CAB-LA as PrEP

Regimen	Singapore	DHHS 2022	IAS 2022	EACS 2022	WHO 2021
TFV (TDF or TAF) # PLUS	If ART is to be started prior to the availability of HIV genotypic resistance testing results				

Regimen	Singapore	DHHS 2022	IAS 2022	EACS 2022	WHO 2021
FTC or 3TC PLUS DRV/r					

TFV: Tenofovir; TDF: Tenofovir disoproxil fumarate; TAF: Tenofovir alafenamide; FTC: Emtricitabine; 3TC: Lamivudine; DRV/r: Darunavir/ritonavir; EACS: European AIDS Clinical Society; IAS: International AIDS Society; DHHS: Department of Health and Human Services; WHO: World Health Organisation
#TDF to be avoided in patients with CrCl <60 mL/min. TAF to be avoided in patients with CrCl <30 mL/min

Principles of ART selection

Most international guidelines recommend ART regimens based on the following guiding principles:[10-12, 26]:

- Effectiveness of the ART regimen
- Safety profile
- Barrier to resistance
- Dosing frequency
- Pill burden
- Drug-drug interactions
- 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[27]. 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 means testing outcomes[27, 28].

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) – as a component of the single-tablet combination TAF/FTC/BIC (Biktarvy™) 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[29]. 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 important not to compromise on clinical outcomes while minimising patients' expenses. One way to reduce the overall cost borne by patients is to optimise and rationalise the use of 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 did not appear to benefit from further CD4 cell count testing overall.[30] Another laboratory test recommendation which can be adjusted for use 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)[31]. 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[10-12, 26]. 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[32]. Singapore's transmitted drug resistance data was provided to the NHIVP by the National Public Health Laboratory (NPHL) during the development of these updated NHIVP ART Recommendations. 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 6.0% in 2020 and 13.8% in 2022. Likewise the prevalence of NNRTI transmitted drug resistance has increased from 2.3% in 2018 to 4.6% in 2020 and 6.4% in 2022. There has also been an increasing trend in NRTI resistance, which increased from 0.8% in 2018 to 7.4% in 2022. In addition, the inclusion of DTG in the subsidized drug list has made INSTI- based regimens increasingly affordable[28]. 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[33, 34]. As such, given the price and dosing advantage of DTG-based regimen, RAL has also been removed from the alternative first line regimen in the 2023 review of the ART recommendations. 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 fumarate (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.[35] 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.[35] 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.[35] 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[35].

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[36].

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[37]. 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[35, 38]. 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 INSTI-based regimen may be associated with early cardiovascular disease. A prospective, multicentre, collaboration study between 17 pre-existing European and Australian cohorts involving more than 32,000 people living with HIV found that INSTI initiation was associated with increased incidence of cardiovascular disease in the first 2 years of exposure (incidence rate of 8.46 events per 1000 person-years of follow up) compared to those without INSTI exposure (incidence rate of 4.19 events per 1000 person-years of follow up), even after adjustment for cardiovascular disease risk confounders[39]. This risk decreases with increasing exposure of INSTI, eventually reaching similar levels to those who were not exposed[39]. However, there are also studies that contradict this finding of increasing cardiovascular risk factors with INSTI use[40]. More studies are required to investigate this association between cardiovascular risk factor and INSTI use.

There are initial concerns that DTG-based regimens may be associated with an increased risk of neural-tube defects (NTD) when used at the time of conception.[41] In view of this, several international guidelines previously recommended that DTG be avoided in women who want to conceive.[10-12, 26] However, other studies (including the ADVANCE study in South Africa) have shown no higher rates of adverse pregnancy outcomes with the use of DTG.[42] 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.[43] In view of this, the WHO 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.[44] 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.[10] 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 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.[45] In addition, BIC was well tolerated with better gastrointestinal tolerability as compared to DTG.[45] 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.[46]

The other advantage of BIC-based regimen is that unlike ABC/3TC/DTG, TAF/3TC/BIC does not require HLA B*57:01 testing. 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.[47]

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.[28] BIC-based regimens are also associated with weight gain.[37] In a pooled analysis of eight randomised controlled trials in ART-naïve individuals, the weight gain between DTG-and BIC- based regimens were similar.[37] 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.[48] 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.[48] No instance of emergent INSTI or NRTI resistance was seen in both treatment groups.[48] 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.[48]

DTG/3TC, co- formulated as a single combination tablet known as Dovato®, is now widely available in Singapore. This combination is also covered under the subsidised drug list, making it a cost-effective option with the advantage of reduced pill burden.

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, we also recommend DTG/3TC as a first line regimen for these individuals.

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.[10-12, 26] 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.[49] 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.[50] 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.[10, 26] 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.[51, 52] 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.[51, 52] 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.[53] 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.[54] 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.[54] 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.[55] 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.[55] DOR has not yet been compared with INSTI. DOR is currently still not widely unavailable in Singapore and hence is not included in the recommendations.

<u>Individuals who acquire HIV while on long acting cabotegravir as PrEP</u>

The use of long acting injectable cabotegravir (CAB-LA) and RPV as treatment for HIV have been approved for use in Singapore since 2022[56]. The use of CAB-LA as pre-exposure prophylaxis (PrEP) however, is still not available in Singapore. Outside Singapore, three countries have approved the use of CAB-LA as PrEP, including the United States of America (USA), Australia and Zimbabwe[57]. It is therefore possible for patients to access CAB-LA as PrEP prior to acquiring HIV, and physicians must check with patients for prior use of CAB-LA use in all newly diagnosed patients.

The prior use of CAB-LA as PrEP may result in the presence of INSTI resistance in newly diagnosed patients. In the HPTN 083 trial, the use of CAB-LA was studied as PrEP in cisgender men who have sex with men (MSM) and transgender women who have sex with men[58]. INSTI-based resistance was detected in 1 of the 4 cases identified as baseline infection and in 4 of the 9 cases identified as incident cases[58]. One case of HIV acquisition occurred during the oral cabotegravir lead in phase which also had INSTI resistance[58]. No INSTI resistance was detected if HIV acquisition occurred during the period of cabotegravir decay[58]. In the HPTN 084 trial, which studied the use of CAB-LA as PrEP in women, four HIV infections occurred in the CAB-LA arm, of which three were identified as incident infections[59]. No INSTI resistance was identified in all four cases. However, two of the cases never received CAB-LA and all the cases had low or unquantifiable CAB levels[59].

Hence, in view of the above, we recommend the use of TFV (TDF or TAF) with 3TC or FTC combined with DRV-r as first line regimen in individuals who had prior CAB-LA exposure, but need to be started on ART prior to the availability of the HIV genotypic resistance testing results (Table IV). If the genotypic resistance testing results do not show INSTI resistance, physicians can consider switching to an INSTI-based regimen after discussion with their patients.

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 regimens have been moved from being a first line regimen recommendation to an 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.[35] 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[51, 52] 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.[60] 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.[61, 62] 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).[63] 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.[64] 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.[64]

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.[49, 60] The same virologic efficacy has also been demonstrated in RPV if the pre-treatment HIV viral load is less than 100,000 copies/ml.[51, 52] 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 6.4% in 2022.

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.[37, 38] 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.[29] 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.[10-12, 26] As they are potent hepatic CYP 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 recommend 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.[65]

DRV/r was compared to ATV/r and RAL in the open label phase 3 ACTG 5257 trial, where 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 compared to ATV/r. Overall however, RAL was superior to both PIs in terms of a composite endpoint of virologic efficacy and tolerability.[66] This was also seen in the FLAMINGO trial, where a DTG-based regimen was superior to DRV/r-based regimen in terms of both virologic efficacy and tolerability at 48 weeks.[67] Hence, considering the points above, 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 PIs.

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 TDF/3TC combination is not available as a single tablet.

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.[68] 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.[69, 70] In addition, TDF has been associated with a decline in bone mineral density (BMD), especially when compared to ABC.[71] There have also been cases of osteomalacia reported with TDF use.[72, 73] 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.[73] In view of this, most international guidelines advise that TDF-containing regimens should be avoided in individuals whose CrCl is below 60mL/min.[10-12, 26] 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 to TAF or TDF combined with EVG treatment. At 144 weeks, TAF had less impact than TDF on bone mineral density and renal biomarkers.[74] When compared to the TDF group, no participants had to discontinue TAF due to renal adverse effects.[74] This observation was also seen in other trials.[75, 76] The same benefits were also noted when switching from TDF- to TAF-based regimens. 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.[77] 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.[37, 78] 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.[79] In view of this, most international guidelines advise that HLA B*57:01 testing should be performed before the use of ABC.[10-12, 26] 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.[31] 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.[31]

Prescribers should take into account other data from Asia suggesting that testing for HLA B*57:01 is optional only in those of Han Chinese ethnicity.[80] 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.[81] Hence, in contrast to international guidelines, the national recommendations suggest HLA B*57:01 testing prior to the use of ABC only for non-ethnically Chinese patients, including patients of lndian and Malay ethnicity with late-stage HIV infection (CD4 < 200 cells/mm^3) (Table II), and that the decision to test before initiation of treatment be made on a case-by-case 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.[82, 83] There were other trials that also replicated this finding.[84, 85] However, there are also studies that did not show this association, including a United States FDA meta-analysis of 26 trials that evaluated ABC.[86, 87] 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.[10-12, 26] 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).[88] 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 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.[65] The exception to this 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.[35] 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[89]. 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.

<u>Comparing ABC/3TC versus TDF/FTC</u>

TDF/FTC and ABC/3TC treatment 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 compared to TDF/FTC, regardless of whether the third active drug was EFV or ATV/r.[49] 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 V-VIII):

   (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
   (E) Switching from a three-drug regimen to a two-drug regimen in the setting of individuals who are stably suppressed on their current regimens with pre-existing or historical M184 V/I mutation resistance.
   (F) Switching from a three-drug regimen to a long-acting ART regimen of injectable CAB and RPV given every 1 or 2 months.

3) In the setting of existing NRTI resistance, switching to a regimen containing TAF or TDF with 3TC or FTC, combined with an ART with a high barrier to resistance such as either DTG, DRV-r or BIC can be considered if necessary.

4) Physicians should switch patients out of 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.

5) If patients are unable to tolerate NRTI-based regimens, physicians can consider using a two-drug regimen instead (Table VII). Possible combinations which 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.

SWITCHING ANTIRETROVIRAL REGIMENS

(A) Table V: 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 fumarate; 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

(B) Table VI: 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	

INITIAL DRUG	REASON TO SWITCH (EXAMPLES)	SWITCH TO	IF	WHEN TO SWITCH
	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

(C) Table VII: 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				

(D) Table VIII: Switching from a three-drug regimen to a two-drug regimen (PO/IM)

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 • Patient with HBV co-infection, 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			
Oral three-drug regimen	Reduce pill burden Improve adherence	IM CAB/RPV	• Patients with HBV co-infection should not be placed on this regimen • No baseline resistance to either drug component	

INITIAL DRUG	REASON TO SWITCH (EXAMPLES)	SWITCH TO	IF	WHEN TO SWITCH
			• Not pregnant or intending to become pregnant	
TDF: Tenofovir disoproxil fumarate. TAF: Tenofovir alafenamide. ABC: Abacavir; DTG: dolutegravir. 3TC: lamivudine RPV: Rilpivirine; CAB: cabotegravir. 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 the 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 <u>patients without any documented drug resistance or history of treatment failure.</u>

Switching NRTI backbone (Refer to Table V)

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.[90, 91] 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.[91] 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.[77] 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.[77, 90, 91]

Switching the third drug (Table VI)

<u>Switching within the same class</u>

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[50]. 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.[92] 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.[51, 52]

  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.[93] In addition, it is also associated with increased virologic failures and drug mutations compared to a PI regimen.[93] 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 VII).

  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.

<u>Switching to a different class of ARV (Refer to Table VI)</u>

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.[94] 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.[95] 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.[96]

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 the presence of chronic kidney diseases places them at higher risk of myocardial infarction, which also precludes the use of ABC- based regimens.[97] 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 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 ART 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 either randomized to the 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 found to be non-inferior to TAF-based regimen, with 93% of participants in both arms maintaining virologic suppression[98]. None of the participants in DTG/3TC arm met virologic withdrawal criteria and no emergent resistance was noted.[98] 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.[98] 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.[48, 98] 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 the DTG/3TC group.

Switching to DTG/3TC has also been studied in patients with multiple or prior virological failures with prior historic and current M184V/I mutation. In the SOLAR 3D study, 100 participants who were virologically suppressed for more than 6 months minimally with prior virological failures, were switched to DTG/3TC. Prior virological failures were defined as having 3 or more prior ART with at least of the following: failure to achieve viral load less than 50 copies/ml, confirmed rebound viral load > 200 copies/ml or documented genotypic/phenotypic resistance. 50 of the participants had historic M184V/I mutations and 50 of the participants did not have historic M184V/I mutation. At week 48, 92% of individuals with historic M184V/I mutation and 88% of individuals without historic M184V/I mutation in the intention to treat population achieved HIV-1 RNA < 50 copies/ml[99]. There were no cases of confirmed virologic failures across treatment arms and no cases of treatment-emergent resistance[99]. However, while the inclusion criteria for the study were participants who were virologically suppressed for more than 6 months, the median duration of viral suppression was 11.8 years[99]. In view of this, physicians should discuss the limitations of the findings with patients before switching suitable individuals who have been stably suppressed on ART for at least 6 months with prior or historic M184V/I mutation to DTG/3TC on a case-by-case basis.

- 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.[100]

- 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.[101] 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.[101]

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 (IM) CAB and RPV.[102, 103] Both the ATLAS and FLAIR trials, which recruited almost 1200 participants, demonstrated non-inferiority of intramuscular CAB/RPV when compared to the three oral drugs standard of care.[102, 103]. In the ATLAS trial, 5 participants in the long-acting therapy group and 3 in the oral therapy group had HIV-1 RNA levels of 50 copies per millimetre or higher (adjusted difference, 0.6 percentage points; 95% CI, -1.2 to 2.5) at week 48, meeting criteria for non-inferiority[102]. Likewise, in the FLAIR trial, 6 participants in the long-acting therapy group versus 7 participants in the oral therapy group had HIV-1 RNA levels greater than 50 copies per millimetre at week 48 (adjusted difference, -0.4 percentage points; 95% CI, -2.8 to 2.1), hence also meeting criteria for non-inferiority[103]. Virologic failure occurred infrequently in both trials; 3 participants in the ATLAS trial and 4 participants in the FLAIR trial. Both trials reported the presence of resistance to NNRTIs and INSTIs in these participants[102, 103]. Predictors of failures included presence of RPV-associated mutations, HIV-1 subtype A6/A1, higher baseline body mass index (BMI) (typically greater than 30 kg/m^2) and lower trough RPV concentrations at week 8[104]. In both trials, adverse events were more frequent in the long-acting ARV group, mainly attributable to injection-site reactions, which occurred in 83% of participants in the long-acting group of the ATLAS trial and in 96% of the participants in the long-acting group of the FLAIR trial[102, 103]. Despite this, both trials reported a greater improvement from baseline in treatment satisfaction in the long-acting therapy group as compared to the oral therapy group[102, 103]. A subsequent trial, ATLAS-2M, also showed the non-inferiority of administering IM CAB/RPV every 8 weeks versus every 4 weeks[105]. The safety profile was similar between the two groups[105].

The ATLAS, FLAIR and ATLAS-2M trials all included a one-month oral lead-in period with oral CAB/RPV before switching to IM CAB/RPV for participants in the long-acting group. However, in week 100 of the FLAIR study, participants in the oral comparator ART group, in discussion with the investigator, could elect to switch to long-acting CAB/RPV via direct to injection or with a 4-week oral lead in or withdraw from study[106]. 232 (92%) of the participants switched to IM CAB/RPV, with 111 participants in the direct to injection group and 121 participants in the oral lead in group. At week 124, switching to long- acting treatment with oral lead-in phase had similar safety, tolerability, and efficacy as the direct to injection group[106].

IM CAB/RPV, along with oral CAB, were approved in Singapore on 5 July 2022 for treatment of HIV in adults who are virologically suppressed on a stable ART regimen with no past or present evidence of resistance to NNRTI or INSTIs[56]. In addition to the above, physicians should select individuals who have good engagement with care, no baseline resistance to either medication, no active or occult HBV infection, who are not pregnant or intending to get pregnant and who are not receiving medications with potential drug-drug interactions with IM CAB/RPV for switch to IM CAB/RPV. The decision to include an oral lead-in period or not prior to IM CAB/RPV should be discussed individually with patients. Patients should be informed of the risk of virologic failure with possible development of resistance if they miss doses or discontinue therapy without an oral replacement therapy. Oral bridging therapy should be made available for planned or inadvertent missed doses. Individuals who choose to stop IM CAB/RPV should be transitioned to an oral ART regimen within 4 weeks of the last monthly IM CAB/RPV dosing or within the last 8 weeks of the last 2-monthly IM CAB/RPV

dosing. Physicians should also note that IM CAB/RPV is not yet available on the subsidised drug list and hence is considerably more costly than the oral regimens in Singapore.

Potential strategies in individuals with NRTI resistance

Several studies involving switching ART in individuals with pre-existing NRTI resistance suggest that combinations containing ARV with high barrier to resistance, with or without fully active NRTIs, may be effective. In the DAWNING study, 624 adults with at least 6 months of treatment with a first-line treatment containing an NNRTI and two NRTI with virological failure (confirmed HIV-1 RNA ≥400 copies per mL) were recruited. 312 participants were randomly assigned to the DTG group and 312 participants were assigned to the ritonavir-boosted lopinavir (LPV/r) group. These were combined with an investigator-selected dual NRTI background regimen with at least one fully active NRTI based on genotypic resistance testing at screening. At week 48, 84% of the participants in the DTG group achieved HIV-1 RNA < 50 copies/ml compared with 70% of the participants in the LPV/r group (adjusted difference 13·8%; 95% CI 7·3-20·3)[107]. In the NADIA trial, 464 participants with virological failure while on NNRTI-based regimens (combined with TDF and either 3TC or FTC), were randomised to receive either DTG or DRV/r, with each arm being further randomised to receive either TDF/3TC or ZDV/3TC. 86% of individuals have an M184V/I mutation while 50% of individuals have K65R mutation. 37% of individuals had dual NRTI resistance. At week 48, 90.2% in individuals in the DTG group and 91.7% of individuals in the DRV/r group achieved a viral load of less than 400 copies/ml (difference, −1.5 percentage points; 95% CI, −6.7 to 3.7), meeting the criteria for non-inferiority[108]. More than 90% of individuals who were taking either DTG or DRV/r and had no NRTIs predicted to have activity had a viral load of less than 400 copies/ml[108]. DTG-associated mutation was detected in 4 patients in the DTG group, but no DRV/r related mutations were detected in the DRV/r group[108]. In addition, a viral load of less than 400 copies/ml was found in 92.3% of individuals in the tenofovir group and 89.6% of individuals in the zidovudine group (difference, 2.7 percentage points; 95% CI, −2.6 to 7.9), meeting the criteria for non-inferiority[108]. This response was also seen in individuals with K65R mutation or intermediate to high level tenofovir mutation at baseline[108].

In view of the above, physicians can consider switching individuals with NRTI resistance to the combination of TAF or TDF plus 3TC or FTC, combined with a fully active third drug with a high genetic barrier to resistance, such as DTG, DRV/r or BIC, if needed. The reasons for switching to a partially active NRTI regimen may include the avoidance of drug-drug interactions, simplification of regimens, a more favourable side-effect profile, amongst other clinical considerations. We do not recommend the use of a regimen with no fully active NRTI if there are other viable options. Further studies are required before this strategy can be used routinely.

Monitoring

Table IX: Monitoring parameters in HIV-infected individuals (1)

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 Note on cost-effectiveness of	

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**
		NB Please refer to main text for discussion					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]								
¥ HIV viral load monitoring should be performed 4 to 8 weeks after switching to IM CAB/RPV								

Table X: 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							

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**
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 XI: 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		√				√	√	

TDF: Tenofovir; HAND: HIV-associated neurocognitive disorders; DTG: dolutegravir

*These are suggested minimum investigations for individuals on ART. Please refer to the National HIV Program Primary Care Recommendations for more comprehensive guide on the primary care of people living with HIV.

Some points to note on monitoring parameters in patients with HIV infection:

HIV viral load and CD4 cell count monitoring

The plasma HIV-1 RNA level, or the viral load, is the most important indicator to monitor response to ART and should be monitored at entry into care, initiation of ART, 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.[109, 110] 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.[111, 112] 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.[30, 113] 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.[10, 11, 26]

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.[10-12, 114] 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.[115] 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.[10-12] 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.[116] Hence, the national recommendations recommend that anti-*Toxoplasma* IgG antibody 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.[117]

Section 4: Antenatal and Perinatal Care of Women Living with HIV

Part A: Antenatal care

1. All women should be offered HIV screening at their first antenatal review.
2. Women with a negative HIV result in the first trimester who are at increased risk of acute HIV infection should undergo repeat testing in the third trimester.

These risks include active injecting drug use, new sexually acquired infection during pregnancy, partner with unknown HIV status or known HIV infection but not virologically controlled (defined as HIV RNA viral load > 200 copies/ml). [3, 4]

3. HIV screen should also be repeated at any time when a woman presents with a new sexually acquired infection at any point of their pregnancy or with signs and symptoms of acute HIV infection.
4. Women who are at increased risk of acute HIV infection should be referred for consideration of pre-exposure prophylaxis (PrEP) if their HIV screen is negative. [118]
5. All HIV screening tests reported as "reactive" or with "confirmatory tests pending" should be assumed to be positive for the purposes of initial management discussions.
6. HIV screening tests reported as "indeterminate" or "inconclusive" should have a HIV viral load performed as soon as possible and referred to an infectious diseases specialist for further management.
7. For late second trimester and all third trimester presentations, referrals to infectious diseases should be made urgently to initiate appropriate treatment and plan peri-partum/post-partum care. Referral to an obstetrician experienced in caring for women living with HIV, and an early consultation with a paediatric infectious diseases specialist should also be considered.

Part B: Intra-partum care

1. Women who present in labour without prior documentation of HIV status should undergo urgent HIV screening. Rapid HIV test can be considered if available. However, the medical team should be aware of the window period of the rapid test used, and nucleic acid testing should be considered in situations where the exposure to HIV was more recent (further information can be obtained from the NHIVP National HIV Testing Recommendations [119]). Women at increased risk of HIV infection whose first trimester test was negative should also undergo urgent screening in labour if a third trimester HIV test has not already carried out.
2. The following individuals should receive intravenous zidovudine in labour or at least 3 hours prior to scheduled caesarean delivery [120, 121]:

Individuals who <u>should</u> receive intravenous zidovudine	**Individuals who <u>do not need</u> intravenous zidovudine**
a. Women with HIV RNA > 1000 copies/ml or have an unknown HIV viral load close to delivery (within 4 weeks of delivery)	a. Women receiving combination ART regimens and have HIV RNA </=50 copies/ml consistently during late pregnancy and near delivery (within 4 weeks of delivery), and where there are

Individuals who <u>should</u> receive intravenous zidovudine	**Individuals who <u>do not need</u> intravenous zidovudine**
b. Women with suboptimal adherence to antiretroviral therapy since their last HIV viral load results c. Women with a positive expedited HIV antigen/antibody screening test result during labour d. In women whose HIV RNA is between 50 to 999 copies/ml within 4 weeks of delivery, IV zidovudine may be considered after discussion with the infectious diseases physician [122].	no concerns regarding adherence to the regimen.

Dose of intravenous zidovudine:

- IV Zidovudine should be started when patients present in labour or at least 3 hours prior to scheduled caesarean delivery.
- Loading dose: 2mg/kg/hr over 1 hour, followed by:
- Maintenance dose: 1mg/kg/hr until delivery (minimum of 3 hours total predelivery)
- For scheduled caesarean delivery, a minimum of 3 hours infusion prior to delivery is recommended based on a pharmacokinetic study that suggests that systemic and intracellular zidovudine levels stabilised after 3 hours of infusion.
- Infusion of zidovudine can be stopped once the umbilical cord is clamped..
- If urgent unscheduled caesarean delivery is indicated in a patient with HIV RNA >1000 copies/ml, shortening the interval between initiation of intravenous zidovudine and delivery may be considered. Some experts recommend administration of the 1-hour loading dose of intravenous zidovudine before proceeding with delivery if an expedited delivery is indicated.

3. In individuals who should receive IV zidovudine, who also have known or suspected zidovudine resistance, intrapartum use of IV zidovudine is still recommended in reducing the risk of perinatal HIV transmission, unless a documented history of hypersensitivity exists.
4. Scheduled caesarean delivery to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral drugs [123].
5. For women with HIV RNA ≤1000 copies/mL, the mode of delivery should be individualized after discussion with an obstetrician. There is limited evidence to suggest that scheduled

caesarean delivery performed solely for the prevention of perinatal HIV transmission is of any benefit, and should not be routinely recommended [123, 124].

6. Foetal scalp electrodes and other invasive sampling methods should not be used during delivery. Artificial rupture of membranes should be avoided unless delivery is imminent or if indicated for augmentation of labour with oxytocin.

Part C: Post-partum care

1. Newborns should be thoroughly washed to remove maternal blood and secretions. Any neonatal issues should be managed as per usual practice.
2. Neonatal ART should be started as close to the time of birth as possible, ideally within 4 - 6 hours of birth.
3. We recommend that women living with HIV not breastfeed their infants; however, we recognise that decisions about infant feeding are highly individualised and should be made in discussion with the parent, the infectious diseases physician, and the neonatologist or paediatrician.
4. FBC and HIV DNA PCR should be sent from infants within 1 month of delivery. Physicians can consider monitoring bloods for infants who are started on combination ART.
5. *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis is not required unless HIV infection is confirmed in the infant.
6. Infants should be managed according to their risk of transmission as indicated below (including breastfeeding status) [125-128]:

Neonatal anti-retroviral management according to risk of perinatal HIV infection

Level of Perinatal HIV Transmission Risk	**Clinical Features**	**Recommended Neonatal ART**	**Recommended Duration**
Low risk	1) Mother is on combination ART and HIV viral load is <50 RNA copies/mL at or after 36 weeks' gestation **and** there are no concerns about adherence 2) If the infant is born prematurely (<34 weeks) but most recent maternal HIV viral load is <50 HIV RNA copies/mL.	Zidovudine (PO/IV) is recommended as soon as possible after birth, and preferably within 4-6 hours after birth. **For dosing in full term infant AND ≥35 weeks' gestation at birth:** • PO 4 mg/kg/dose or IV 3 mg/kg/dose, twice daily • PO 4 mg/kg/dose twice daily or if unable to tolerate orally, IV 3 mg/kg/dose, twice daily **For dosing in premature infant:** **a) <35 weeks' gestation at birth:** • Birth – 2 weeks: PO 2 mg/kg/dose or IV 1.5mg/kg/dose, twice daily • Age > 2 weeks: PO 3 mg/kg/dose or IV 2.3mg/kg/dose, twice daily **b) <30 weeks' gestation at birth:** • Birth – 4 weeks: PO 2 mg/kg/dose or IV 1.5mg/kg/dose, twice daily • Age > 4 weeks: PO 3 mg/kg/dose or IV 2.3mg/kg /dose, twice daily	4 weeks
High risk	For infants born to mother with: • No receipt of antepartum and/or intrapartum ART • Started ART late (<12 weeks before delivery) • Poor adherence or uncertainty about adherence	**Three-drug combination regimen of Zidovudine PLUS Lamivudine PLUS Nevirapine is recommended.** See respective dosing below: **Zidovudine (PO/IV):** See dosing above.	6 weeks

Level of Perinatal HIV Transmission Risk	Clinical Features	Recommended Neonatal ART	Recommended Duration
	to ART in the 12 weeks before delivery, or • Maternal HIV RNA >50 copies/ml at close to delivery • Individuals with unconfirmed HIV status **OR** who have at least one positive HIV test at delivery or post-partum	**Lamivudine (PO):** • Birth – 4 weeks: PO 2 mg/kg/dose, twice daily • Age > 4 to 6 weeks: PO 4 mg/kg/dose, twice daily **Nevirapine* (PO):** • <34 weeks' gestation at birth: ➢ Birth to 2 weeks: 2 mg/kg/dose, twice daily ➢ Age > 2 to 4 weeks: 4 mg/kg/dose, twice daily • ≥34 to <37 weeks' gestation at birth: ➢ Birth to 6 days: 4 mg/kg/dose twice daily ➢ Age 1 to 4 weeks: 6 mg/kg/dose twice daily • ≥37 weeks' gestation at birth: ➢ Birth to 4 weeks: 6 mg/kg/dose twice daily	6 weeks 4 weeks

*Nevirapine should be stopped 2 weeks before other concurrent ART to reduce risk of Nevirapine monotherapy and drug resistance development due to its long half-life

Maternal post-partum care

- If the mother received IV zidovudine, this can be stopped once the umbilical cord is clamped.
- All components of the mother's ART regimen should be continued on schedule
- Individualised contraceptive counselling should be given to mothers as part of postpartum care

Part D: Infant monitoring and immunisations

- Blood investigations to monitor the infant for adverse events of ART are not routinely recommended, unless there is clinical suspicion for a drug-related adverse event.
- All infants born to mothers with HIV should have HIV proviral DNA tested at 4-8 weeks of age and then again at 4-6 months of age. HIV antibodies should be tested for at 15-18 months of age. Additional testing will be required if infants are breastfed.
- HIV proviral DNA testing may be performed earlier if there is clinical suspicion or if there is very high risk of perinatal transmission.
- Immunisations:
    - Routine immunisation schedules should be followed.
    - BCG and Hepatitis B should also be administered.
    - Inactivated Polio vaccine (e.g. 5-in-1 or 6-in-1) can be safely administered.
    - Rotavirus vaccines can be safely administered to infants born to mothers with HIV.

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National HIV Programme

ART Recommendations Workgroup Terms of Reference (FY2023 – 2025)

Membership

The Antiretroviral Therapy (ART) Recommendations Workgroup is a select group of stakeholders who are involved in the work of HIV prevention and care management. Members are chosen based on their expertise in the relevant fields to join the National HIV Programme (NHIVP)'s efforts in coordinating the national HIV response. This Terms of Reference is effective from 1 April 2023 – 31 March 2025, unless terminated by agreement between the parties.

The workgroup comprises of:

- Dr Ho Lai Peng, Senior Principal Medical Social Worker, NCID
- Ms Law Hwa Lin, Senior Principal Pharmacist (Specialist), NCID
- Dr Dariusz Olszyna, Director, EHIVP, NUH
- Dr Tham Sai Meng, Associate Consultant, Infectious Diseases, NUH
- Ms Joy Yong, Principal Clinical Pharmacist, NUH
- Ms Virginie Forget, Senior Medical Social Worker, NUH
- Dr Teh Yii Ean, Director, EHIVP, SGH
- Dr Nathalie Chua, Specialist Pharmacist, SGH
- Ms Jasmin Foong, Senior Medical Social Worker, SGH
- Dr Edwin Sng, Director, EHIVP, CGH
- Mr Wilson Lee, Senior Pharmacist, CGH
- Ms Fadhiilah Binte Ismail, Medical Social Worker, CGH
- Dr Asok Kurup, Infectious Diseases Specialist, Infectious Diseases Care Pte Ltd
- Dr Li Jiahui, Consultant, Paediatrics Infectious Diseases, KKH
- Prof Chong Chia Yin, Senior Consultant, Paediatrics Infectious Diseases, KKH
- Dr Rina Ong, Specialist Pharmacist, KKH
- Dr Valerie Seah, Specialist Pharmacist, KKH
- Dr Chan Si Min, Senior Consultant, Paediatrics Infectious Diseases, NUH
- Dr Rie Aoyama, Consultant, Paediatrics Infectious Diseases, NUH
- Dr Olivia Leow, Consultant, Paediatrics Infectious Diseases, NUH

Purpose

The ART Recommendations Workgroup serves to provide the NHIVP with input and guidance regarding the prescription of ARTs in Singapore. To be effective, the workgroup will adopt the following operating procedures:

1. Providing input on the current ART prescribing practices
2. Adapting international guidelines to the local context
3. Drafting the National HIV Programme's ART Recommendations
4. Review all written materials for quality assurance
5. Utilising local data to inform ART prescribing practices

Responsibilities, Powers and Procedures

1. Members will participate in email communications, and in-person meetings upon request.
2. The NHIVP Executive will act as secretariat to the workgroup and will:
    - Develop and disseminate meeting schedules
    - Consult with the workgroup to determine meeting topics and agenda
    - Organises presentations for meetings where relevant
    - Manage online communication and dissemination of relevant information
    - Record and distribute meeting minutes
    - Act as the main point of contact for programme-related questions or issues

3. Members' responsibilities are to:
    - Attend all workgroup meetings, or where attendance is not possible, submit an apology
    - Participate actively and work cooperatively with other members
    - Prepare for all meetings by reading and considering the agenda items, papers circulated and other relevant documents
    - Provide a review of current materials for adaptation to the Singapore context
    - Advice on implementation of initiatives in Singapore
    - Respect group procedures, decisions and diverging opinions expressed by other members
    - Agree to the workgroup's privacy and confidentiality agreement

Remuneration

Workgroup members are requested to participate voluntarily. No sitting fees will be provided.

Privacy and Confidentiality

To ensure effective consultation between the NHIVP and the workgrup members, sensitive information that is not available in the public domain may sometimes be disclosed and shared at workgroup meetings or through emails on a confidential basis. This includes discussions on the group's mailing list. Members are expected to be mindful of the confidentiality of this information and should not disclose them to outside parties.

If members are unsure about the confidentiality status of specific information or data disclosed to them, the Chair (Director, National HIV Programme) should be consulted for clarification.

A/Prof Sophia Archuleta
Director
National HIV Programme
National Centre for Infectious Diseases

Financial Disclosure

Workgroup Member	Financial Disclosure	
	Company	**Relationship**
Sophia Archuleta	None	N/A
Wong Chen Seong	Gilead	Advisory Board, Research Funding
	GSK/Viiv	Advisory Board
Choy Chiaw Yee	GSK ViiV	Speaker
Lavinia Lin	None	N/A
Sally Low	None	N/A
Ho Lai Peng	None	N/A
Law Hwa Lin	None	N/A
Dariusz Olszyna	Gilead	Advisory Boards and Consultancy; Travel and Subsistence Fees
	GSK/ViiV	
	Janssen / Johnson & Johnson	Travel and Subsistence Fees
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Asok Kurup	None	N/A
Li Jiahui	None	N/A
Chong Chia Yin	Moderna	Honorarium for speaker
Rina Ong Yue Ling	None	N/A
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