Antiretroviral therapies

for treating Human Immunodeficiency Virus type 1 (HIV-1) infection

Technology Guidance from the MOH Drug Advisory Committee

Guidance recommendations

The Ministry of Health's Drug Advisory Committee has recommended the following antiretroviral therapies (ARTs):

- ✓ **Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs):** lamivudine 150 mg tablet, tenofovir disoproxil fumarate 300 mg tablet, zidovudine 100 mg capsule;
- ✓ **Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** efavirenz 200 mg and 600 mg tablets, etravirine 200 mg tablet, nevirapine 200 mg and 400 mg tablets, rilpivirine 25 mg tablet;
- ✓ **Protease inhibitors (PIs):** atazanavir 200 mg and 300 mg capsules, darunavir 600 mg and 800 mg tablets, lopinavir 200 mg/ritonavir 50 mg tablet and lopinavir 80 mg/ritonavir 20 mg oral solution, ritonavir 100 mg tablet;
- ✓ **Integrase strand transfer inhibitors (INSTIs):** dolutegravir 50 mg tablet, raltegravir 400 mg and 600 mg tablets; and
- ✓ **Fixed-dose combinations:** abacavir 600 mg/lamivudine 300 mg tablet, abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg tablet, emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg tablet

in line with their registered indications for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection.

Subsidy status

Raltegravir 400 mg and 600 mg tablets, and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg tablet are recommended for inclusion on the Medication Assistance Fund (MAF) in combination with other antiretroviral agents for the treatment of HIV-1 infection.

All other abovementioned ARTs are recommended for the inclusion on the MOH Standard Drug List (SDL).

SDL subsidy or MAF assistance **do not** apply to any other ARTs that are not listed above.

Details of all recommendations are provided in the Annex.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of antiretroviral therapies (ARTs) for treating Human Immunodeficiency Virus type 1 (HIV-1) infection. The Agency for Care Effectiveness conducted the evaluation in consultation with senior healthcare professionals from public healthcare institutions experienced in the treatment of individuals living with HIV-1 infection. Published clinical and economic evidence for all ARTs was considered in line with their registered indications. The use of ARTs for pre-exposure prophylaxis (PrEP) was outside the scope of the evaluation.

1.2 The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3 Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1 The Committee acknowledged that ARTs are standard of care for treating HIV infection, however, none of them are currently included in the MOH List of Subsidised Drugs, representing a therapeutic gap.

2.2 Early treatment with ARTs is recommended in clinical guidelines to delay the onset of acquired immune deficiency syndrome (AIDS), reduce morbidity and mortality, and prevent HIV transmission in the community. In local practice, initial ART regimens for treatment-naive individuals generally consist of backbone therapy with two nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), plus a third drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI). Treatment regimens are individualised for each patient, with ART selection guided by many factors including virologic efficacy, adverse effects, pill burden, dosing frequency, drug-drug interaction, comorbid conditions, cost, childbearing potential and drug resistance.

2.3 The Committee considered advice from local experts that there was limited clinical need to consider dual ART regimens and CCR5 antagonists for subsidy as they are not widely used in Singapore and are not included in local clinical guidelines.

2.4 The Committee noted that there are approximately 6,500 individuals living with HIV in Singapore, and agreed that there was a high clinical need to consider ARTs for subsidy to improve treatment affordability and ensure appropriate patient care.

Clinical effectiveness and safety

3.1 The Committee acknowledged that most NRTIs, NNRTIs and PIs are listed in the WHO Model List of Essential Medicines, and available clinical evidence has consistently shown that they reduce morbidity and mortality in treatment naïve and treatment experienced individuals living with HIV.

3.2 The Committee reviewed the available evidence for INSTIs (dolutegravir, bictegravir, raltegravir and elvitegravir), a newer class of ART. While there was a lack of head-to-head trials comparing them with each other, pairwise trial comparisons and a network meta-analysis suggested that all INSTIs were non-inferior in terms of viral suppression (proportion of patients achieving HIV RNA < 50 copies/ ml through weeks 48 and 96) and tolerability, with dolutegravir and bictegravir demonstrating a higher barrier to resistance. The Committee noted that findings were consistent with recommendations from overseas HTA agencies, such as PBAC (Australia) and CADTH (Canada), which had also considered all INSTIs were comparable in terms of efficacy and safety.

3.3 Overall, the Committee agreed that all INSTIs had an acceptable safety profile. While trials showed that individuals who received dolutegravir had less adverse events that affect the central nervous system (CNS) compared with efavirenz (an NNRTI), the Committee considered that the results were not clinically significant, and noted that CNS adverse events were manageable and generally mild.

Cost effectiveness

4.1 The Committee heard that cost effectiveness results from overseas HTA agencies were generalisable to the local context and it was likely that all ARTs could be considered cost-effective or even cost saving with the availability of generics, given that most local prices were comparable or cheaper than prices in overseas high income countries (including Australia and South Korea).

4.2 All manufacturers were invited to submit value based pricing (VBP) proposals for their products for subsidy consideration. Some manufacturers declined to have their products considered and subsequently could not be recommended by the Committee (Annex).

4.3 The Committee agreed that a cost-minimisation approach was appropriate to select drugs within each class for subsidy in view of their comparable efficacy and safety. On the basis of acceptable cost-effectiveness and low risk of misuse, the Committee agreed that SDL listings were appropriate for NRTIs, NNRTIs, and PIs. For INSTIs, the Committee recommended that the least expensive product (dolutegravir) could be listed on SDL, and the next least expensive one (raltegravir) could be listed on MAF to provide an alternative treatment option.

Estimated annual technology cost

5.1 The Committee noted that the annual cost impact to list 22 recommended ART preparations on SDL or MAF was more than SG$10 million in the first year of listing.

Additional considerations

6.1 Given that emtricitabine/tenofovir disoproxil fumarate is also approved for pre-exposure prophylaxis (PrEP), which was outside the scope of the evaluation, the Committee considered that an MAF listing for the treatment of HIV-1 infection only was necessary to ensure clinical governance.

Recommendation

7.1 Based on available evidence, the Committee recommended for 22 ART preparations (Annex) to be listed on SDL or MAF for treating HIV-1 infection in line with their registered indications, in view of the current therapeutic gap in the MOH List of Subsidised Drugs and acceptable clinical and cost effectiveness at the prices proposed by the manufacturers.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Recommendation
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	
Abacavir 300 mg tablet	Not recommended for subsidy
Lamivudine 150 mg tablet	SDL
Lamivudine 10 mg/mL oral solution*	Not recommended for subsidy
Tenofovir disoproxil fumarate 300 mg tablet	Reclassified from MAF to SDL
Zidovudine 100 mg capsule	SDL
Zidovudine 10 mg/mL oral solution*	Not recommended for subsidy
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Efavirenz 200 mg tablet	SDL
Efavirenz 600 mg tablet	SDL
Etravirine 200 mg tablet	SDL
Nevirapine 200 mg tablet	SDL
Nevirapine 400mg extended release tablet	SDL
Rilpivirine 25mg tablet	SDL
Protease inhibitors (PIs)	
Atazanavir 200 mg capsule	SDL
Atazanavir 300 mg capsule	SDL
Darunavir 600 mg tablet	SDL
Darunavir 800 mg tablet	SDL
Indinavir 200 mg capsule	Not recommended for subsidy
Lopinavir 200 mg/ritonavir 50 mg tablet	SDL
Lopinavir 80 mg/ritonavir 20mg per mL oral solution	SDL
Ritonavir 100 mg tablet	SDL
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir 50 mg tablet	SDL
Raltegravir 400 mg tablet	MAF ***MAF criteria:*** In combination with other antiretroviral agents for the treatment of HIV-1 infection
Raltegravir 600 mg tablet	
CCR5 antagonist	
Maraviroc 150 mg tablet*	Not recommended for subsidy
Maraviroc 300 mg tablet*	Not recommended for subsidy
Fixed-dose combinations	
Abacavir 600 mg/lamivudine 300 mg tablet	SDL
Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg tablet	SDL
Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide fumarate 25 mg tablet	Not recommended for subsidy
Dolutegravir 50 mg/rilpivirine 25 mg tablet	Not recommended for subsidy
Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide fumarate 10 mg tablet	Not recommended for subsidy

Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg tablet	Not recommended for subsidy
Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg tablet	Not recommended for subsidy
Emtricitabine 200 mg/tenofovir alafenamide fumarate 10 mg tablet	Not recommended for subsidy
Emtricitabine 200 mg/tenofovir alafenamide fumarate 25 mg tablet	Not recommended for subsidy
Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg tablet	MAF ***MAF criteria:*** In combination with other antiretroviral agents for the treatment of HIV-1 infection
Lamivudine 150 mg/zidovudine 300 mg tablet	Not recommended for subsidy

* manufacturers did not want products to be considered for subsidy listing

About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. The guidance is based on the evidence available to the Committee as at 20 March 2020. This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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