Original Article

Prevalence of Abacavir Hypersensitivity Reaction and Cost-Effectiveness of HLA-B*5701 Screening: A Ten-Year Experience in The HRH Princess Maha Chakri Sirindhorn Medical Center

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Background: Recently, the authors had reported a case with abacavir hypersensitivity reaction (ABC-HSR), the first diagnosed patient at the HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC). There was no data regarding the incidence or prevalence of ABC-HSR previously reported in Thailand.

Objective: To study the prevalence of ABC-HSR, the abacavir use pattern and the cost effectiveness for the routine human leukocyte antigen (HLA)-B*5701 screening before abacavir use by analyses of the MSMC data.

Materials and Methods: All patients at the MSMC who were prescribed abacavir from October 1, 2010 to September 30, 2020 were retrospectively reviewed for ABC-HSR and the abacavir use pattern at the time when abacavir was started. The cost-effectiveness analysis was applied by analyzing the cost between the routine HLA-B*5701 screening before abacavir use and the HLA-B*5701 confirmation for ABC-HSR. The cost for the prevention of a case of ABC-HSR was defined.

Results: There were total of 54 patients who were prescribed abacavir and only one ABC-HSR case diagnosed. The prevalence of ABC-HSR was 1.85%. The main reason for the abacavir prescription was a substitution for tenofovir (TDF) because of the TDF adverse effects (81.13%). The HLA-B*5701 screening before abacavir use was done in 26.42% at the MSMC. If all eligible patients were routinely screened for the HLA-B*5701 allele before abacavir use, the cost would be 54,000 Baht. The cost for the diagnosis and the management of the ABC- HSR case was 7,230 Baht. The cost for the prevention of a case of ABC-HSR was 46,770 Baht.

Conclusion: The prevalence of ABC-HSR was low. The main reason for abacavir use was a substitution for TDF. The cost for the prevention for a case of ABC-HSR was 46,770 Baht which would be less if the cost for the HLA-B*5701 test was reduced.

Keywords: Abacavir; Hypersensitivity reaction; Prevalence; HLA-B*5701

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Recently, the authors had reported a case with abacavir hypersensitivity reaction (ABC-HSR) who was the first diagnosed patient at the HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC)[1]. This situation prompted the actions to review the occurrence of ABC-HSR especially for its prevalence and its use in the MSMC. Abacavir was firstly prescribed in 2010 at the MSMC and continued to be used regularly until the present time.

ABC-HSR is a life-threatening condition which usually occurs in the first 6 weeks of initiation of abacavir[2]. Hetherington S, et al reported the incidence of ABC-HSR to be 4.3%[2]. The incidence or prevalence of ABC-HSR in Thailand is still unknown.

ABC-HSR can be prevented by screening with the blood test for human leukocyte antigen (HLA)-B*5701 allele before the use of abacavir[3-5].

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The occurrence of HLA-B*5701 allele varied among populations. The studies from Thailand reviewed the low prevalence of the HLA-B*5701 allele in the Thai population which was lower than the prevalence in the Caucasian population[6-8].

Routine HLA-B*5701 screening before abacavir use is recommended in the standard guidelines for the management of human immunodeficiency virus (HIV) infected persons worldwide[9,10]. Although, the current Thailand National Guidelines for the Management of HIV Infected Persons recommends either using HLA-B*5701 as a screening test or monitoring clinical presentation for ABC-HSR after using it[11].

The clinical observation was a considerable choice since the screening test of HLA-B*5701 allele might not be cost-effective in the Thai population given the lower prevalence of HLA-B*5701 allele[6]. The current cost for the HLA-B*5701 screening test is 1,000 Baht/test[12]. Some patients still cannot afford the cost for the HLA-B*5701 screening before the use of abacavir because this cost is not included in the free treatment package.

Abacavir was introduced into the Thai HIV treatment guideline as an alternative drug for the patients who cannot tolerate with the standard treatment regimen in the year 2008[13]. The most recent data of abacavir prescriptions in Thailand (as of March 2021) was 13,422 cases according to the letters from the Thai National Health Security Office (NHSO) secretary[14] and the Thai Social Security Office (SSO) secretary[15]. Among 13,422 cases, there were 7,915 universal coverage (UC) cases[14]; 3,656 social security scheme (SSS) cases[15]; 1,226 Civil Servant Medical Benefit scheme (CSMBS) cases[14]; and 625 other cases[14]. According to this significant use, the cost effectiveness analysis for the HLA-B*5701 screening before abacavir use should be prominent.

Objective

The authors would like to define the prevalence of ABC-HSR, reviewing the authors' experience of abacavir use pattern in the MSMC and analyzed for the cost effectiveness of the routine use of the blood test for the HLA-B*5701 screening before abacavir use by analysis of the MSMC data.

Materials and Methods

Study design

The present study was the retrospective observational study in the HIV infected patients of the MSMC with the age of more than or equal to 18 years-old who was prescribed abacavir between October 1, 2010 and September 30, 2020. The data were collected from the MSMC computerized database and all medical charts reviewed at the time when abacavir was started.

Population

Inclusion criteria: All HIV infected patients of the MSMC with the age of more than or equal to 18 years-old who were prescribed abacavir between October 1, 2010 and September 30, 2020.

Exclusion criteria: The patients who took abacavir for less than 6 weeks and did not have ABC-HSR or the patients who had the HIV treatment for less than 6 weeks during the study period.

Case identification

The patient diagnosed with ABC-HSR would have at least two findings of these symptoms or tests:

- Fever
- Rash
- Gastro-intestinal symptoms included nausea, vomiting, diarrhea or abdominal pain
- Fatigue or myalgia
- Respiratory symptoms included cough, shortness of breath or pharyngitis or abnormal laboratory tests included abnormal liver function test, increased creatinine phosphokinase level, lymphopenia or abnormal chest radiograph[11].

Statistical and data analysis

The patient characteristics which were univariable and categorical variable data were described in number and percentage. The continuous variable data which had normal distribution were described by mean ± standard deviation (SD). The continuous variable data but not normal distribution was presented with median with interquartile range. The incomplete data would be deleted and were not included for calculation.

The prevalence of ABC-HSR was described by descriptive analysis using the percentage of the outcome. These data were from all ABC-HSR cases divided by all abacavir cases.

The abacavir use pattern was described by retrospectively descriptive analysis using the percentage of the reason for abacavir use at the time when abacavir was started and the percentage of the HLA-B*5701 screening done before the use of abacavir. The incomplete data would be deleted and not involved in the data calculation.

The cost of the routine HLA-B*5701 screening before abacavir use was described by using the

total cost predicted if all cases prescribed for abacavir during the study period were tested for the HLA-B*5701 screening tests. The cost for the HLA-B*5701 screening test is the national reference cost of this test[12]. The cost for the diagnosis and the management of the ABC- HSR case was described by the real cost occurred and calculated from the reported ABC-HSR case of the MSMC. The cost effectiveness for routine HLA-B*5701 screening before abacavir use was defined by the cost for the prevention of a case of ABC-HSR occurred at the MSMC. This cost was calculated by all the cost predicted in the routine HLA-B*5701 screening before abacavir use minus the cost predicted for the diagnosis and the management of all the ABC-HSR cases if the screening was not done then divided by the total number of ABC-HSR cases.

Ethics approval

The present study received the approval from the Srinakharinwirot University Ethics Committee on March 6, 2020, and the approval for the adjustment of the project on November 2, 2020. The ethics committee number was SWUEC/E-356/2562.

All patients were informed and consented to have their medical records reviewed and data published.

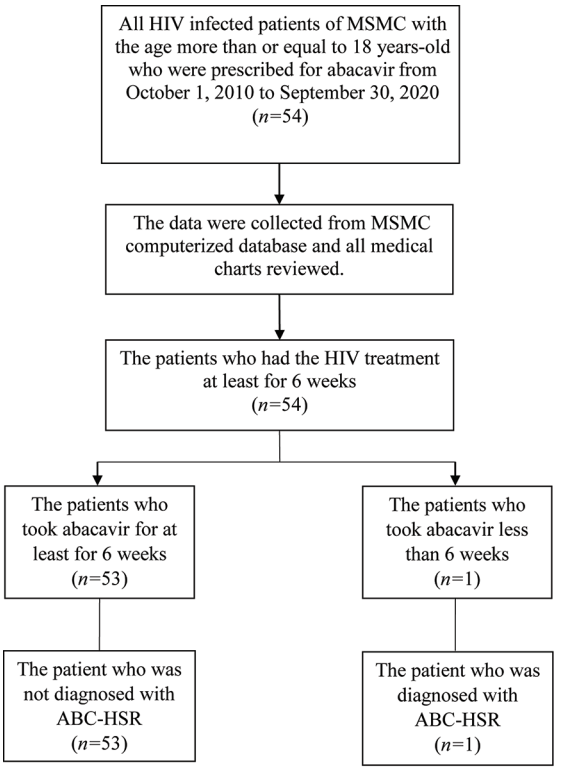

Figure 1. The study flowsheet.

Results

There were total of 54 patients who were prescribed abacavir during the study period. All patient data were collected from the MSMC computerized database and all medical charts at the time when abacavir was started. Most of them were on treatment for more than 6 weeks with only one who was on abacavir for less than 6 weeks. The one case who was on abacavir for less than 6 weeks was the one who developed ABC-HSR whose information and outcome had been described in the previous published case report[1]. The study flowsheet was presented in Figure 1.

Patient Characteristics: There were total of 41 males (75.93%) and 13 females (24.07%) in the present study. The mean weight was 63.18 kilogram. The patients' hometowns were: Bangkok (5, 9.26%), the central region (28, 51.85%, included 14 from Pathum Thani, 8 from Nakhon Nayok, 2 from Nakhon Pathom, 1 from Ayutthaya, Nakhon Sawan, Saraburi, and Uthai Thani), the eastern region (17, 31.48%, included 8 from Prachin Buri, 3 from Chon Buri, 2 from Chanthaburi and Chachoengsao, 1 from Rayong, and Sakaeo), the southern region (3, 5.56%, included 1 from Krabi, Phatthalung, and Surat Thani) and the northern region (1, 1.85% from Uttaradit). The Medical Benefit Scheme were the CSMBS (28; 51.85%), the UC (12; 22.22%), the SSS (7, 12.96%), the state-owned enterprise Scheme (4, 7.41%), and their own-payment (3, 5.56%). The most common co-morbidities were hyperlipidemia (20), hypertension (15), diabetes mellitus (15), chronic renal insufficiency (11), hepatitis (5), cardiovascular disease (2), and malignancy (1). The mean time from the first antiretroviral regimen to the abacavir containing antiviral regimens was 7.31 (SD 5.32) years.

The mean of their CD4 cell counts was 485.90 cell/mm^3, SD 260.85 (23.24%, SD 9.26%). There were 5 missing CD4 cell counts and 6 missing CD4 cell counts percentage data during a year on the abacavir containing antiviral regimens. Most of the patients had suppressed HIV viral load during a year on their abacavir containing antiviral regimens. About 98%, the HIV viral load were undetectable (either <40 copies/mL or <20 copies/mL depended on the test done). The only one who had a detectable viral level was 117 copies/mL and later became undetectable. There were 4 missing HIV viral load data during a year on the abacavir containing antiviral regimens.

Table 1. The patient characteristics

	n (%)
Sex (case)	
Male	41/54 (75.93)
Female	13/54 (24.07)
Mean age (year)	51.52 (SD 8.96)
Mean weight (kg)	63.18 (SD 11.36)
Mean height (cm)	164.13 (SD 7.86)
Patient's hometowns (case)	
Bangkok	5/54 (9.26)
Central Region	28/54 (51.85)
Eastern region	17/54 (31.48)
Southern region	3/54 (5.56)
Northern region	1/54 (1.85)
Medical Benefit Scheme	
Civil Servant Medical Benefit Scheme	28/54 (51.85)
Universal Coverage (NHSO)	12/54 (22.22)
Social Security Scheme (SSO)	7/54 (12.96)
State-owned Enterprise Scheme	4/54 (7.41)
Own payment	3/54 (5.56)
Most common co-morbidities (case)	
Hyperlipidemia	20/54 (37.04)
Hypertension	15/54 (27.78)
Diabetes mellitus	15/54 (27.78)
Chronic renal insufficiency	11/54 (20.37)
Hepatitis	5/54 (9.26)
Cardiovascular disease	2/54 (3.70)
Malignancy	1/54 (1.85)
HIV viral load (case)	
Not detected	27/50 (54.00)
Detectable (<20 copies/mL)	4/50 (8.00)
Detectable (<40 copies/mL)	18/50 (36.00)
Detectable (≥40 copies/mL)	1/50 (2.00)
Mean CD_4 (cells/mm^3)	485.90 (SD 260.85)
Mean %CD_4 (%)	23.24 (SD 9.26)
Mean time from first antiretroviral regimen to the abacavir containing antiviral regimens (year)	7.31 (SD 5.32)

NHSO=National Health Security Office; SSO=Social Security Office; SD=standard deviation

All their subsequent HIV viral loads were suppressed. All patient characteristics were described in Table 1.

There was only one case of ABC-HSR diagnosed during the study period. Therefore, the prevalence of ABC-HSR in the MSMC was 1.85% (1/54). The main reason (root cause analysis) for the prescription of abacavir was a substitution for tenofovir (TDF) because of tenofovir adverse effects (81.13%, 43/53).

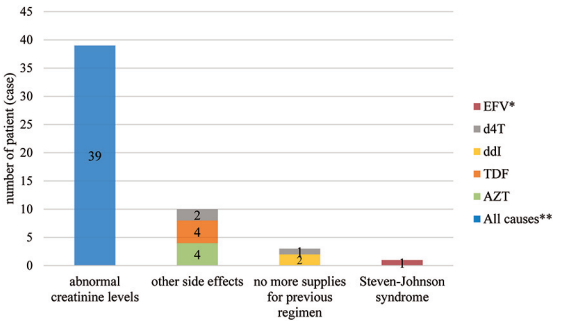

Figure 2. The reasons for abacavir use.

EFV=efavirenz; d4T=stavudine; ddI=didanosine; TDF=tenofovir disoproxil fumarate; AZT=zidovudine

* Substitution for EFV in the year 2001. ** All causes such as co-morbidities (hypertension, diabetes mellitus or chronic renal insufficiency), TDF induced nephrotoxicity or unknown causes that TDF should be avoided or discontinued.

The reasons for abacavir use were abnormal creatinine levels of all causes (73.58%, 39/53) such as co-morbidities (hypertension, diabetes mellitus or chronic renal insufficiency), TDF induced nephrotoxicity or unknown causes that TDF should be avoided or discontinued, other side effects (3 zidovudine induced macrocytic anemia, 2 lipoatrophy from zidovudine and stavudine, 1 stavudine induced pancreatitis, 1 TDF induced osteopenia, 1 osteonecrosis of hips on TDF, 1 TDF related nausea/vomiting and 1 TDF related anorexia/ weight lost) from previous regimens (18.87%, 10/53), no more supplies for the previous regimens (2 didanosine and 1 stavudine) (5.66%, 3/53) and efavirenz induced Steven-Johnson syndrome (1.89%, 1/53). The one missing data was a case who was prescribed abacavir at another hospital and was later referred to the MSMC without the switching information included. The reasons for abacavir use were shown in Figure 2.

The MSMC data showed that there were only 26.42% (14/53) of patients who were tested for the HLA-B*5701 screening before abacavir use. Most of the patients (73.58%; 39/53) who were prescribed abacavir were monitored for the clinical presentation of ABC-HSR after using abacavir.

All HLA-B*5701 tests done in the MSMC during the present study period were also monitored to find the possible cases tested positive before abacavir use and did not receive abacavir. There were total of 27 tests done during the present study period and there was only one positive test which was the test from the reported ABC-HSR case[1].

At present, the outcomes of the present study patients were 9 deaths. The causes of deaths were

Table 2. The MSMC cost effectiveness analysis data

HLA-B*5701 screening before abacavir use	HLA-B*5701 screening tests		Diagnosis and management of the ABC-HSR		Total cost*
	Cost/case	Number of patients	Cost/case	Number of patients	
Yes	1,000 Baht	54	7,230 Baht	0**	54,000 Baht
No	1,000 Baht	0	7,230 Baht	1***	7,230 Baht
The cost for the prevention of an ABC-HSR case in MSMC					46,770 Baht

HLA=human leukocyte antigen; ABC-HSR=abacavir hypersensitivity reaction; MSMC=HRH Princess Maha Chakri Sirindhorn Medical Center

* Total cost=the cost of HLA-B*5701 screening tests plus the cost of diagnosis and management of the ABC- HSR

** If everyone who received abacavir was screened with HLA-B*5701 before starting abacavir, there would be no case of ABC-HSR

*** According to the MSMC data, the prevalence of ABC-HSR in the MSMC was 1.85% (1/54), there was only one case of ABC-HSR diagnosed

malignancy (4/9), cerebrovascular diseases (2/9), renal failure (2/9) and bacterial sepsis (1/9).

The cost effectiveness analysis for the routine HLA-B*5701 screening before abacavir use, if all these 54 patients were tested for the HLA-B*5701 screening before abacavir use, there would be no ABC-HSR case diagnosed at the MSMC. The cost for the tests would be 54,000 Baht (54×1,000). If all these 54 patients were not tested for the HLA-B*5701 screening before abacavir use, there would be one ABC-HSR case occurred. Using the authors' computerized data, the authors calculated for the real cost happened in the reported MSMC ABC-HSR case. The costs included basic laboratory tests, supportive care (IV fluid + medication) and a blood test for HLA-B*5701 allele (for the confirmation of ABC-HSR diagnosis). The total cost was 7,230 Baht. Therefore, the cost for the prevention for an ABC-HSR case at the MSMC should be 54,000 minus 7,230 equals to 46,770 Baht. The MSMC cost effectiveness analysis data was presented in Table 2.

Discussion

In January 2021, the authors reported a patient with ABC-HSR with the confirmation by a positive blood test for HLA-B*5701 who was the first ABC-HSR diagnosed at the MSMC (June 2019)[1]. The information of this case, ABC-HSR and HLA-B*5701 test reviews and discussion were described in the author's previous published case report[1]. After this diagnosis, all patients who received abacavir containing antiretroviral regimens in the MSMC, during the ten years timing, were reviewed to define the prevalence of ABC-HSR since this prevalence was unknown in Thailand. The authors were also interested in the abacavir use pattern in the MSMC and the possibility to define the cost effectiveness for the routine use of the HLA-B*5701 screening before abacavir use.

At present, there were at least 13,422 patients taking abacavir for management of HIV infection in Thailand[14,15]. This number could be under-estimated since the abacavir use data information from the CSMBS (1,226 persons)[14], the state-owned enterprise scheme and the own-payment (625 persons)[14] parts were not well recognized. The trend for abacavir use in Thailand would be slowly increased since more patients could not tolerate with TDF adverse effects would emerge[16].

Although ABC-HSR is a life-threatening condition, the mortality rate was reported to be only 0.03%[2]. The most importance issue for the management of ABC-HSR was early diagnosis and abacavir discontinuation before the symptoms progressed[1]. ABC-HSR could be prevented by screening with the blood test for the HLA-B*5701 allele before abacavir use[3-5]. Realization of ABC-HSR manifestation would be crucial in the setting that the HLA-B*5701 screening could not be done before abacavir use[1].

The risk to develop ABC-HSR varied among population which was 3% in the Black population and 6% to 8% in the others[17,18]. For Thailand, there were no reports of the ABC-HSR incidence or prevalence so far. The evidence of the risk to develop ABC-HSR was related to the presentation of the HLA-B*5701 allele since only less than 1% of the sub-Saharan and the East Asian had this allele while 5% to 8% of the Caucasians were positive for this gene[19-22].

There were some reported data for the presentation of HLA-B*5701 allele which was around 0.55% to 10% of the Thai population[6,7,19,23]. The presentation of the HLA-B*5701 allele in Thailand was different among the regions which were 5% in Bangkok, 2% in the central region, 1% in the north-eastern region, 0.67% in the northern region and 0.5% in the southern region[8]. To the authors' knowledge, these data might be closely referred to the risk to develop ABC-HSR

in the Thai population. The prevalence of ABC-HSR as of 1.85% reported in the present study should be related to the distribution of the different hometowns among the MSMC patient-cohort.

Abacavir is currently listed as an alternative medicine for substitution of TDF in case one cannot tolerate with the adverse effects of TDF[11]. The most common adverse effect of TDF is nephrotoxicity[11,16]. The present study data showed the main reason for abacavir use was for the substitution of TDF in those patients who developed abnormal kidney function tests while taking TDF. The other reasons were the bone issues (TDF related osteopenia and avoiding TDF in case who developed bilateral osteonecrosis of hips), the gastro-intestinal adverse effects (severe nausea and vomiting) and the anorexia and weight lost complaint which were improved after the discontinuation of TDF.

At present, there is only zidovudine to be used as an alternative for TDF or abacavir[11]. With the introduction of tenofovir alafenamide fumarate to the Thai HIV management guideline in the near future, there will be more options to be considered. Although, abacavir is currently a preferable alterative medication for TDF[11].

The current Thai National HIV Management Guideline recommends either using HLA-B*5701 allele as a screening test or monitoring clinical presentation for ABC-HSR after using it[11]. The use of the HLA-B*5701 screening is still depended on the clinician's opinion. The present study data suggested that only 26.42% of the patients being prescribed abacavir were tested for the HLA-B*5701 allele before abacavir use. The opinions varied among the authors' four Infectious Diseases Specialists. The opinions included 2 for using the HLA-B*5701 screening in all cases before abacavir use, 1 for not using the HLA-B*5701 screening at all (only monitoring for the clinical presentation for ABC-HSR) and 1 for using the HLA-B*5701 screening only in some cases who can afford the test cost.

According to the cost effectiveness issue, there were some data regarding the cost effectiveness for the use of the HLA-B*5701 screening before abacavir use in Singapore[24] and Korea[22]. Kapoor et al reported that it was not cost effective to test for the HLA-B*5701 screening before abacavir use for all diverse ethnics in Singapore, except for the early-stage Indian HIV patients who were contraindicated to TDF group[24]. The prevalence of the positive HLA-B*5701 allele among the diverse ethnics were 1.1% in the Chinese, 1.8% in the Malay and 6.3% in the Indian[24]. A study from Park et al showed that for the Korean population which had the prevalence of the HLA-B*5701 allele at the rate of 4%, the HLA-B*5701 screening might not be cost-effectiveness[22].

The use of the HLA-B*5701 screening before abacavir use would have some impact on the Thai health system. The authors would like to apply the MSMC cost effectiveness analyses data to calculate for the cost of the tests involved in the national level to show this impact. According to the data, there were 13,422 patients currently received abacavir in Thailand[14,15]. If all these patients were tested for the HLA-B*5701 screening before abacavir use, the cost would be 13,422,000 Baht. If the HLA-B*5701 screening before abacavir use was not done in every person, there should be at least 249 ABC-HSR occurred (13,422×0.0185=248.307). The cost for the diagnosis and the management of the ABC-HSR cases would be 1,800,270 Baht (7,230×249=1,800,270). The cost saved if not routinely tested for the HLA-B*5701 screening before all abacavir use would be 11,621,730 Baht (13,422,000–1,800,270=11,621,730). The impact on the Thai health system would be in the ten million Baht range if the HLA-B*5701 screening before abacavir use would be routinely done.

If the cost of the HLA-B*5701 screening could be reduced by half to 500 Baht/test, it would be the great impact on the cost effectiveness issue. The cost for screening all patients with the HLA-B*5701 tests would be reduced to 6,711,000 Baht (13,422×500=6,711,000). The cost for the diagnosis and the management of ABC- HSR cases would able the same at 1,800,270 Baht. The cost for the prevention for a case of ABC-HSR would be reduced to 19,721.81 Baht (6,711,000–1,800,270=4,910,730; then divided by 249 equals to 19,721.81). If the cost for the HLA-B*5701 screening could be reduced even more, the cost for the prevention for a case of ABC-HSR would decrease further.

Conclusion

The prevalence of ABC-HSR was low. The main reason for using abacavir was a substitution for TDF. The cost for the prevention for a case of ABC-HSR was 46,770 Baht which would be less if the cost for the HLA-B*5701 test was reduced.

What is already known on this topic?

The prevalence of ABC-HSR in Thailand was unknown. Abacavir is an alternative for TDF in the management of HIV-infected patients. There was no data regarding the cost effectiveness of the

HLA-B*5701 screening before abacavir use in Thailand.

What this study adds?

The prevalence of ABC-HSR was 1.85% and the cost for the prevention for a case of ABC-HSR was 46,770 Baht which would be less if the cost of the HLA-B*5701 test was reduced.

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Conflicts of interest

The authors declare no conflicts of interest.

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