*HLA-B*5701* Genotyping for Abacavir Prescription: Re-Examination of its Cost-Effectiveness in Singapore

Dear Editor,

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) that is used to control disease progression of human immunodeficiency viruses (HIV). It reduces the morbidity and mortality of HIV infections.[1] A serious side effect of abacavir is hypersensitivity reaction (HSR) which usually begins within 6 weeks of starting treatment and manifests as fever, malaise, nausea, vomiting and rashes. In severe cases, it results in multiple organ system failure.[2]

Patients with *HLA-B*5701* polymorphism are more likely to develop HSR.[3] Studies from several countries have demonstrated the efficacy of screening for this polymorphism prior to abacavir prescription.[4,5] A large-scale clinical trial has provided strong evidence to order *HLA-B*5701* genotyping prior to abacavir prescription and to avoid this drug in patients who carry the polymorphism.[6]

We need to assess the cost-effectiveness of screening tests such as *HLA-B*5701* genotyping even when they are shown to be clinically useful.[7] An assessment of the cost-effectiveness of *HLA-B*5701* genotyping before abacavir prescription was carried out in the local context.[8] The parameters used to assess the economic costs of the test include the additional cost of genotyping, prescription of expensive alternative antiretroviral therapy drugs in allele-positive patients, the burden of additional expenses and the loss of health that may be incurred after no such test was carried out. The report concluded that *HLA-B*5701* genotyping was not cost-effective in Singapore except for a specific subgroup of newly diagnosed Indian patients with early-stage HIV in whom tenofovir was contraindicated.

Since the publication of the results of that study, new information on *HLA-B*5701* genotyping has become available that includes the actual price of the test in Singapore, genotype frequency in a real cohort of patients and the actual costs of managing adverse reactions based on physicians' input. We attempted to ascertain whether refinement of data in the cost-effectiveness model would change the conclusions. To ensure consistency with our previous work, we retained the TreeAge model and same data where no new information was available.[8]

Materials and Methods

Our institutional review board verified that ethics review was not needed for this study. Patient data from Tan Tock Seng Hospital (TTSH) was anonymised. In TTSH, most infectious disease physicians order *HLA-B*5701* genotyping when they prescribe abacavir. The Clinical Immunology Laboratory in TTSH has been offering the test since 2015. Information on ethnicity and *HLA-B*5701* status of patients was provided by the laboratory without identifiers. The genotype frequency of Chinese (n = 758), Malay (n = 164) and Indian (n = 53) patients was 0.26%, 2.44% and 15.10%, respectively.

Patients were segmented according to early- and late-stage disease. Similar to the earlier study, late-stage HIV infection is defined as CD4 count <200/μL.[9] Each group was further divided based on tenofovir contraindications into 2 groups: 1) patients who contraindicated to tenofovir and were prescribed abacavir, and 2) patients who could be prescribed both abacavir and tenofovir. In the latter, 4 strategies were examined: 1) abacavir was assigned as first-line (without genotyping) treatment with tenofovir as second-line therapy; 2) abacavir was assigned as first-line (with genotyping) treatment with tenofovir as second-line therapy; 3) tenofovir was assigned as first-line treatment with abacavir as second-line (without genotyping) therapy; and 4) tenofovir was assigned as first-line treatment with abacavir as second-line (with genotyping) therapy. In patients whom tenofovir was contraindicated, 2 strategies were investigated: 1) abacavir was assigned as first-line treatment without genotyping, and 2) abacavir was assigned as first-line treatment with genotyping.

Zidovudine was assigned as next-in-line treatment followed by last-line therapy in both patient groups. All 3 NRTI, abacavir, tenofovir and zidovudine were used with lamivudine. The last line of treatment comprised personalised combination of stavudine, lamivudine, emtricitabine, atazanavir, lopinavir and ritonavir.

The treatment costs and cost structures shown in Table 1 were retrieved from the homepage of TTSH and after consultation with infectious disease physicians. Although we mirrored the cost calculations in the study by Kapoor and associates,[8] we have revised the cost structure to better reflect contemporary clinical practice.

The costs of treating side effects of abacavir, tenofovir and zidovudine were calculated using 2 categories of data: 1) public versus private fees for consultations and tests, and 2) inpatient treatment versus outpatient treatment. We have

Table 1. Cost Structures of Inpatient and Outpatient Treatments with Antiretroviral Drugs

Cost Structure	No. of Consultations	Bed Rest Duration (Week)	No. of Full Blood Count Tests	No. of Renal Panel Tests	No. of Liver Panel Tests	No. of Urine and PCR Tests	No. of Blood Transfusions
Outpatient cost of treating side effects of:							
Abacavir	3	–	3	3	3	–	–
Tenofovir	3	–	3	3	3	3	–
Zidovudine	3	–	3	3	3	–	–
Inpatient cost of treating side effects of:							
Abacavir	–	1	7	7	7	–	–
Tenofovir	–	1	7	7	7	2	–
Zidovudine	–	1	7	7	7	–	1

PCR: Polymerase chain reaction

Each treatment strategy takes into account multiple factors including the number of consultation sessions or duration of bed rest and important biochemical tests.

assumed that the outpatient group received 3 consultations and 3 sets of tests—full blood count, liver and renal panel tests—and the inpatient group was hospitalised for 1 week and received 7 sets of tests. Patients on tenofovir were at risk of renal impairment and they were monitored with urinalysis and protein-creatinine ratio determination while those on zidovudine may have required blood transfusions because of anaemia.

For costs that could not be calculated, we relied on data from the study by Kapoor and associates (Table 2),[6,10-15] especially those that pertained to the treatment of abacavir HSR and abacavir-induced fatalities based on studies done in the United States.[10] All financial costs are shown in US currency based on an exchange rate of S$1.26 to US$1.00 which was the rate used by Kapoor and associates in their study.[8]

Like the earlier study, the cost-effectiveness of *HLA-B*5701* screening was performed in early- and late-stage HIV patients independently in the 3 ethnic groups. Although a threshold of US$50,000 for each quality-adjusted life year (QALY) was used to maintain consistency with our earlier study, we were aware that this benchmark is not without controversy. The Patient Protection and Affordable Care Act (PPACA) of the United States has prohibited the use of thresholds[16] and the quantum of US$50,000/QALY has also been questioned.[17] Costs and QALY have not been discounted and were consistent with the methodology used in the earlier study.

Results

Incremental cost-effectiveness ratio (ICER)—defined as difference in costs between 2 interventions divided by the difference in outcomes for each intervention[14]—was used to compare cost savings enjoyed by early- and late-stage HIV patients under each strategy. Regardless of treatment strategy, Tables 3 and 4 showed that abacavir as first-line therapy without genotyping in all early-stage HIV patients in the 3 ethnic groups was the cheapest and most cost-effective treatment, irrespective of contraindication to tenofovir.

In late-stage HIV patients who could be prescribed abacavir and tenofovir, regardless of treatment strategy abacavir as first-line therapy without genotyping remained the cheapest and the most cost-effective treatment in the Chinese. However, for Malays and Indians, abacavir as first-line therapy with genotyping was the cheapest and most cost-effective strategy. Compared to subjects with abacavir without genotyping, their counterparts who underwent genotyping before abacavir enjoyed lower cost and this made it the dominant therapy in this group of patients.

Discussion

Using updated data, we reviewed the cost-benefit ratio of *HLA-B*5701* genotyping before abacavir prescription. Genotyping was not cost-effective prior to abacavir use in early-stage HIV patients in all ethnicities. However, genotyping of late-stage Malay and Indian HIV patients was cost-effective. This finding differs from the conclusion of the study by Kapoor and associates[8] which showed that genotyping was not cost-effective in all patients except for newly diagnosed, early-stage HIV Indian patients who contraindicated to tenofovir. The main reason for different ICER in the Chinese, Malays and Indians could be attributed to the different prevalence of *HLA-B*5701* gene in the 3 ethnicities. The *HLA-B*5701* gene frequencies

Table 2. Variable Values for Base Case and Corresponding Value Ranges for Sensitivity Analysis in Cost-Effectiveness Modelling

Variable	Base Value	Sensitivity Analysis Range	Source
Cost (US$)			
Mean monthly cost of ABC + lamivudine	92	46 – 184	Tan Tock Seng Hospital
Mean monthly cost of tenofovir + lamivudine	319	160 – 638	Tan Tock Seng Hospital
Mean monthly cost of AZT + lamivudine	372	186 – 744	Tan Tock Seng Hospital
Mean monthly cost of EFV	85	42 – 170	Tan Tock Seng Hospital
Mean monthly cost of hypothetical drug	740	370 – 1480	Tan Tock Seng Hospital
Three clinician consultations due to side effects	210	–	Tan Tock Seng Hospital
*HLA-B*5701* genetic test	110	55 – 220	Tan Tock Seng Hospital
Treatment of ABC-HSR cases	1983	959 – 3836	Tan Tock Seng Hospital
Treatment of intolerable side effects of ABC	1918	959 – 3836	Tan Tock Seng Hospital
Fatal ABC-HSR cases	31,600	15,800 – 63,200	Schackman, et al[*]
Treatment of intolerable side effects of tenofovir	3499	1750 – 7000	Tan Tock Seng Hospital
Treatment of intolerable side effects of AZT	3490	1745 – 6980	Tan Tock Seng Hospital
Routine renal panel and urine analyses	47	–	Tan Tock Seng Hospital
Probabilities			
Mild ABC-HSR cases	0.585	–	Eron, et al[†]
Severe non-fatal ABC-HSR cases	0.408	–	Tan Tock Seng Hospital
Intolerable side effects of tenofovir (%)	7	3 – 15	Tan Tock Seng Hospital
Intolerable side effects of ABC (%)	1	0 – 5	Tan Tock Seng Hospital
Intolerable side effects of AZT (%)	1	0 – 5	Tan Tock Seng Hospital
HSR mortality in ABC-HSR cases (%)	0.03	0 – 0.06	Tan Tock Seng Hospital
*HLA-B*5701* genotyping (%)			
Gene frequency in Chinese	0.26	–	Tan Tock Seng Hospital
Gene frequency in Malays	2.44	–	Tan Tock Seng Hospital
Gene frequency in Indians	15.10	–	Tan Tock Seng Hospital
Positive predictive value in suspected cases	61.20	10 – 90	Mallal, et al[‡]
Negative predictive value in suspected cases	95.50	93.3 – 96.7	Mallal, et al[‡]
Quality of life score			
Early-stage HIV cases	0.781	0.616 – 0.946	Kauf, et al[§]
Late-stage HIV/AIDS cases	0.746	0.572 – 0.92	Kauf, et al[§]
Quality of life decrease due to side effects			
Mild HSR	0.08 (for 3 days)	0.08 (for 1 – 7 days)	Dodek, et al[‖]
Severe HSR	0.15 (for 7 days)	0.15 (for 3 – 15 days)	Pepper, et al[¶]
Fatal HSR	0.36 (for 15 days)	0.36 (for 7 – 30 days)	Freedberg, et al[#]
Mean decrease in ABC-HSR cases (except fatal cases)	0.12 (for 5 days)	0.12 (for 3 – 10 days)	–
Tenofovir side effects	0.15 (for 7 days)	0.15 (for 3 – 15 days)	Similar to severe HSR
Zidovudine side effects	0.15 (for 7 days)	0.15 (for 3 – 15 days)	Similar to severe HSR
Abacavir side effects (except HSR)	0.72	(0.36 – 1.44)	Ratio of mild to severe cases = 1:1

ABC: Abacavir; AIDS: Acquired immunodeficiency syndrome; AZT: Zidovudine; EFV: Efavirenz; HIV: Human immunodeficiency viruses; HSR: Hypersensitivity reaction

[*]Schackman BR, Gebo KA, Walensky RP, Losina E, Muccio T, Sax PE, et al. The lifetime cost of current human immunodeficiency virus care in the United States. Med Care 2006;44:990-7.

[†]Eron J Jr, Yeni P, Gathe J Jr, Estrada V, DeJesus E, Staszewski S, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. Lancet 2006;368:476-82.

[‡]Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-79.

[§]Kauf TL, Roskell N, Shearer A, Gazzard B, Mauskopf J, Davis EA, et al. A predictive model of health state utilities for HIV patients in the modern era of highly active antiretroviral therapy. Value Health 2008;11:1144-53.

[‖]Dodek P, Phillips P. Questionable history of immediate-type hypersensitivity to penicillin in Staphylococcal endocarditis: treatment based on skin-test results versus empirical alternative treatment—a decision analysis. Clin Infect Dis 1999;29:1251-6.

[¶]Pepper PV, Owens DK. Cost-effectiveness of the pneumococcal vaccine in healthy younger adults. Med Decis Making 2002;22:S45-57.

[#]Freedberg KA, Losina E, Weinstein MC, Paltiel AD, Cohen CJ, Seage GR, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. N Engl J Med 2001;344:824-31.

Table 3. Cost-Effectiveness of Treatment Strategies in Newly Diagnosed Early- and Late-Stage HIV Patients on Abacavir and Tenofovir

Treatment Strategy	Cost (US$)	Change in Cost	QALY	Change in QALY	ICER (US$/QALY)
Early-stage					
Chinese					
ABC as first-line without genetic screen	68,661	–	23.25458	–	–
ABC as first-line with genetic test	68,853	192	23.25459	0.000013	14,323,794
TDF as first-line (genetic test before ABC)	142,878	74,025	23.25477	0.00018	412,147,302
TDF as first-line	142,958	79	23.25477	-1E – 06	Dominated
Malays					
ABC as first-line without genetic screen	69,743	–	23.25447	–	–
ABC as first-line with genetic test	70,621	878	23.25459	0.000126	6,985,711
TDF as first-line (genetic test before ABC)	143,026	72,405	23.25477	0.000176	412,134,575
TDF as first-line (no genetic test before ABC)	143046	21	23.25476	-0.00001	Dominated
Indians					
ABC as first-line without genetic screen	76,024	–	23.25384	–	–
ABC as first-line with genetic test	80,887	4863	23.25462	0.000778	6,251,947
TDF as first-line (no genetic test before ABC)	143,561	62,675	23.25472	0.000098	637,809,573
TDF as first-line (genetic test before ABC)	143,883	321	23.25477	0.000055	5,865,668
Late-stage					
Chinese					
ABC as first-line without genetic screen	22,954	–	7.459795	–	–
ABC as first-line with genetic test	23,090	136	7.459801	0.000006	23,154,854
TDF as first-line (no genetic test before ABC)	47,794	24,705	7.459782	-1.8E – 05	Dominated
TDF as first-line (genetic test before ABC)	47,804	24,715	7.459783	-1.8E – 05	Dominated
Malays					
ABC as first-line with genetic screen	23,090	–	7.459801	–	–
ABC as first-line without genetic test	23,329	240	7.459746	-5.5E – 05	Dominated
TDF as first-line (genetic test before ABC)	47,804	24,715	7.459783	-1.8E – 05	Dominated
TDF as first-line (no genetic test before ABC)	47,824	24,735	7.459779	-2.2E – 05	Dominated
Indians					
ABC as first-line with genetic screen	23,090	–	7.459801	–	–
ABC as first-line without genetic test	25,509	2420	7.45946	-0.00034	Dominated
TDF as first-line (genetic test before ABC)	47,804	24,715	7.459783	-1.8E – 05	Dominated
TDF as first-line (no genetic test before ABC)	47,999	24,909	7.45976	-0.00004	Dominated

ABC: Abacavir; HIV: Human immunodeficiency viruses; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year; TDF: Tenofovir
The term "dominated" was used to supplant actual negative cost-effectiveness ratio values. These are values in which the alternative strategy in question was more costly and produced fewer QALY.

reported by Kapoor and associates for the Chinese (1.10%), Malays (1.80%) and Indians (6.30%) were different from the findings of this study.

While screening of *HLA-B*5701* was shown to be cost-effective in countries such as the United States[10] and the United Kingdom,[18] differences in cost structures and population genetics mean that such conclusions could not cross national boundaries. Our study also suggests that the conclusions provided by pharmaco-economic analyses will vary across time because of the accumulation of new data and fluctuating test costs and drug prices.

The study has a few limitations. Specific data was derived from published literature cited in the study by Kapoor and associates that were not necessarily specific to Singapore and when we did not have new information. This included quality of life values. Since we used the same model structure

Table 4. Cost-Effectiveness of Treatment Strategies in Newly Diagnosed Early- and Late-Stage HIV Patients Contraindicated to Tenofovir

Treatment Strategy	Cost (US$)	Incremental Costs	QALY	Incremental QALY	ICER (US$/QALY)
Early-stage					
Chinese					
No genetic test	69,557	–	23.25459	–	–
*HLA-B*5701* test	69,764	208	23.2546	0.000014	15,305,250
Malays					
No genetic test	70,834	–	23.25448	–	–
*HLA-B*5701* test	71,861	1026	23.25461	0.000127	8,061,323
Indians					
No genetic test	78,255	–	23.25387	–	–
*HLA-B*5701* test	84,036	5781	23.25465	0.000788	7,336,974
Late-stage					
Chinese					
No genetic test	23,245	–	7.459805	–	–
*HLA-B*5701* test	23,386	141	7.459811	0.000006	23,361,205
Malays					
*HLA-B*5701* test	23,386	–	7.459811	–	–
No genetic test	23,684	298	7.459758	0.000053	Dominated
Indians					
No genetic test	26,234	2848	7.459484	-0.000326	Dominated
*HLA-B*5701* test	23,386	–	7.459811	–	–

HIV: Human immunodeficiency viruses; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year
The term "dominated" was used to supplant actual negative cost-effectiveness ratio values in which the alternative strategy in question was more costly and produced fewer QALY.

as the earlier study, we experienced the same limitations highlighted in the earlier paper including absence of scenarios of drug resistance, toxicity or co-infections and assumption of constancy in the quality of life throughout a HIV patient's life.[8]

Conclusion

HSR and side effects of abacavir impose a need for rigorous monitoring of HIV patients on highly active antiretroviral therapy. This study attempts to reflect actual clinical practice to accurately assess the cost-effectiveness of genotyping. Based on our findings, we recommend genotyping late-stage Malay and Indian patients irrespective of whether they contraindicated to tenofovir. While we are aware that some clinicians adopt the conservative approach of screening patients of all ethnicities, we believe that this study emphasises the need to subject genetics-based screening tests to continual analysis of cost-effectiveness. This study is useful in informing the "Community Blueprint to End HIV Transmission in Singapore" which constitutes part of the national strategy to eliminate HIV infection in Singapore.[19]

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. New Engl J Med 1998;338:853-60.
2. Clay PG. The abacavir hypersensitivity reaction: a review. Clin Ther 2002;24:1502-14.
3. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359:1121-2.
4. Rauch A, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. Clin Infect Dis 2006;43:99-102.
5. Zucman D, Truchis Pd, Majerholc C, Stegman S, Caillat-Zucman S. Prospective screening for human leukocyte antigen-B*5701 avoids abacavir hypersensitivity reaction in the ethnically mixed French HIV population. J Acquir Immune Defic Syndr 2007;45:1-3.
6. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-79.
7. Neymark N. Techniques for health economics analysis in oncology: part 1. Crit Rev Oncol Hematol 1999;30:1-11.
8. Kapoor R, Martinez-Vega R, Dong D, Tan SY, Leo YS, Lee CC, et al. Reducing hypersensitivity reactions with HLA-B*5701 genotyping before abacavir prescription: clinically useful but is it cost-effective in Singapore? Pharmacogenet Genomics 2015;25:60-72.

9. Delpierre C, Dray-Spira R, Cuzin L, Marchou B, Massip P, Lang T, et al. Correlates of late HIV diagnosis: implications for testing policy. Int J STD AIDS 2007;18:312-7.
10. Schackman BR, Gebo KA, Walensky RP, Losina E, Muccio T, Sax PE, et al. The lifetime cost of current human immunodeficiency virus care in the United States. Med Care 2006;44:990-7.
11. Eron J Jr, Yeni P, Gathe J Jr, Estrada V, DeJesus E, Staszewski S, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. Lancet 2006;368:476-82.
12. Kauf TL, Roskell N, Shearer A, Gazzard B, Mauskopf J, Davis EA, et al. A predictive model of health state utilities for HIV patients in the modern era of highly active antiretroviral therapy. Value Health 2008;11:1144-53.
13. Dodek P, Phillips P. Questionable history of immediate-type hypersensitivity to penicillin in Staphylococcal endocarditis: treatment based on skin-test results versus empirical alternative treatment—a decision analysis. Clin Infect Dis 1999;29:1251-6.
14. Pepper PV, Owens DK. Cost-effectiveness of the pneumococcal vaccine in healthy younger adults. Med Decis Making 2002;22:S45-57.
15. Freedberg KA, Losina E, Weinstein MC, Paltiel AD, Cohen CJ, Seage GR, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. N Engl J Med 2001;344:824-31.
16. Neumann PJ, Weinstein MC. Legislating against use of cost-effectiveness information. N Engl J Med 2010;363:1495-7.
17. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796-7.
18. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. Pharmacogenetics 2004;14:335-42.
19. Chan RK. Can we end the human immunodeficiency virus (HIV) in Singapore? Ann Acad Med Singapore 2018;47:499-50.

Kang Shiong Goh, [1]*MBBS*, Ritika Kapoor, [2]*MTech, PhD*, Cheng Chuan Lee, [3]*MRCP (UK), FRCP (Edin), FAMS*, Carol YL Ng, [4]*BSc*, Khai Pang Leong, [3]*FRCPE, FAMS*

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[2]Saw Swee Hock School of Public Health, National University of Singapore, Singapore
[3]Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore
[4]Clinical Immunology Laboratory, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Goh Kang Shiong, Lee Kong Chian School of Medicine, 11 Mandalay Road, Singapore 308232.
Email: kangshiong.goh@mohh.com.sg