HLA: abacavir 2356

CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, HLA = human leukocyte antigen, NS = non-significant, OR = odds ratio, RR = relative risk, S = significant, SmPC = summary of product characteristics

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

Brief summary and justification of choices:
Abacavir can induce hypersensitivity reactions, that can be fatal in severe cases and should be avoided as far as possible. Because specific HLA proteins are involved in specific cellular immune reactions that cause specific hypersensitivity reactions, HLA proteins can affect the risk of hypersensitivity reactions.
All 3 meta-analyses and 9 studies included in the risk analysis investigating HLA and hypersensitivity incidence showed that HLA-B*5701 strongly increased the risk of abacavir hypersensitivity (OR = 8-1,507, RR = 7-55 in mixed or White populations) (Sousa-Pinto 2015, Tangamornsuksan 2015, Cargnin 2014, Saag 2008, Rodríguez-Nóvoa 2007, Stekler 2006, Phillips 2005, Hughes DA 2004, Martin 2004, Hughes AR 2004, Hetherington 2002, and Mallal 2002). A 10th study, not investigating the significance of the association, showed a numerical increase with a factor of 14 (Quiros-Roldan 2020). In addition, the meta-analysis and all 4 included studies comparing HLA-B*5701-guided therapy (i.e. avoidance of abacavir in HLA-B*5701 carriers) with not HLA-B*5701-guided therapy showed HLA-B*5701-guided therapy to significantly reduce abacavir hypersensitivity reactions (Cargnin 2014, Mallal 2008, Waters 2007, Zucman 2007, and Rauch 2006).
Based on these data, the KNMP Pharmacogenetics Working Group concluded that a gene-drug interaction is present and that abacavir should be advoided in HLA-B*5701 carriers (yes/yes-interaction). This concurs with the decision taken in March 2008 by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, in which the Dutch Medicines Evaluation Board (CBG) is represented. The decision recommended that the product information for abacavir must state that patients should be screened to determine whether they are carriers of the HLA-B*5701 allele before starting the treatment and that abacavir should not be used for patients who are carriers of this HLA allele.
You can find an overview of the observed clinical effects in the background information text of this gene-drug interaction in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting abacavir to be essential for drug safety. Genotyping must be performed before drug therapy has been initiated to guide drug selection.
The clinical implication of the gene-drug interaction scores 9 out of the maximum of 10 points (with pre-emptive genotyping considered to be essential for scores ranging from 6 to 10 points) (see also the two tables at the end of this risk analysis):
The risk of serious and possibly life-threatening abacavir hypersensitivity reactions is increased for carriers of HLA-B*5701. The SmPC indicates that abacavir-induced hypersensitivity reaction can be fatal (severity code F, corresponding to CTCAE grade 5). This results in the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for CTCAE grade 5).
The increased risk for serious life-threatening hypersensitivity reactions (code E corresponding to grade 4) has been shown in 9 studies and 3 meta-analyses and the reduction of these serious life-threatening hypersensitivity reactions by avoiding abacavir in HLA-B*5701 carriers has been shown in 4 studies and 1 meta-analysis. This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).
The number needed to genotype was deduced from the largest study comparing HLA-B*5701-guided to not HLA-B*5701-guided therapy (Mallal 2008) to be 31. Four studies (Mallal 2008, Rauch 2006, Zucman 2007 and Waters 2007) showed that prospective screening and exclusion of HLA-B*5701 carriers from abacavir therapy resulted in a decrease in the percentage of patients with abacavir-induced hypersensitivity reactions from respectively 2.7%, 8% and 12% to 0%, and from 7.5% to 2.0%. The HLA-B*5701 carrier prevalence in the studies was respectively 5.6%

(West-Australia), 7.7% (West-Australia), 4.4% (France), and 7.3% (United Kingdom). For the calculation of the number needed to genotype, we used the largest study, which also gave the smallest and thus probably most realistic risk difference (2.7% of patients). This risk difference indicates a number needed to genotype of 37 in a population with a HLA-B*5701 carrier prevalence of 5.6%. The HLA-B*5701 carrier prevalence in the Netherlands is 6.7%. Correction for this slightly higher HLA-B*5701 carrier prevalence, results in a number needed to genotype of 31 in the Dutch population to prevent one patient developing abacavir hypersensitivity. The calculated number to genotype of 31 results in 2 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (2 points for 10 ≤ NNG ≤ 100).
The Summary of Product Characteristics (SmPC) of abacavir indicates that screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin, before initiating treatment with abacavir and that abacavir should not be used in patients known to carry the HLA-B*5701 allele. This results in the maximum number of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (2 points for a recommendation to genotype).
In addition to the clinical implication score indicating pre-emptive genotyping to be essential, 10 out of 12 cost and cost-effectiveness analyses suggest that pre-emptive screening for HLA-B*5701 is cost-saving (4 studies: Manson 2021, Plumpton 2018, Wolf 2010, and Hughes 2004) or cost-effective (6 studies: Zhou 2021, Ruiz-Iruela 2016, Nieves Calatrava 2010 (described in the systematic review of Plumpton 2016), Cargnin 2014, Kauf 2010, and Schackman 2008) at HLA-B*5701 carrier frequencies comparable to those in the Netherlands. Only Kapoor 2015 and Goh 2019 suggest that it is only cost-effective for part of these patients (only for early-stage HIV patients),

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Quiros-Roldan E et al.
Abacavir adverse reactions related with HLA-B*57:01 haplotype in a large cohort of patients infected with HIV.
Pharmacogenet Genomics 2020;30:167-74.
PMID: 32453265.</td><td>3

B*5701: AA</td><td>Data from 1801 patients treated with abacavir and genotyped for HLA-B*5701 were retrospectively analysed. Part of these patients were treated before introduction of the abacavir screening test, and so were only tested afterwards. 1769 patients were HLA-B*5701 negative and the other 32 were HLA-B*5701 positive.
Abacavir hypersensitivity reaction was diagnosed as confirmed when two or more of the following groups of signs/ symptoms were reported: (a) fever, (b) rash, (c) gastrointestinal (nausea, vomiting, diarrhoea or abdominal pain), (d) constitutional (malaise, fatigue, arthralgia, myalgia and general ill feeling) and (e) respiratory (dyspnoea, cough and pharyngitis). Exclusion criteria were the presence of other more likely causes of the hypersensitivity reaction-like event and the absence of adverse events after abacavir re-administration.
No fatal hypersensitivity reactions were described and in all cases symptoms gradually resolved after abacavir discontinuation.
Abacavir hypersensitivity reactions were not immunologically confirmed.
The significance of differences in results between HLA-B*5701 carriers and non-carriers was not determined.

Results for HLA-B*5701 carriers compared to non-carriers (nd = significance not determined):
<table><tr><td></td><td></td><td>value for non-carriers</td></tr><tr><td>% of patients discontinuing abacavir due to adverse events</td><td>x 7.2 (nd)</td><td>9.6%</td></tr><tr><td>% of patients discontinuing abacavir due to clinically confirmed abacavir hypersensitivity reaction</td><td>x 14.3 (nd)
68.8% of the HLA-B*5701 carriers developed a clinically confirmed abacavir hypersensitivity reaction.</td><td>4.8%</td></tr><tr><td>days to abacavir</td><td>x 0.53</td><td>64.2</td></tr></table></td><td>Authors’ conclusion: “191 out of 1801 patients with a known HLA-B*57:01 pattern discontinued abacavir because of toxicity/ intolerance; among them 107 described adverse events fulfilled the criteria of confirmed abacavir hypersensitivity reaction (22/32 allele-positive patients and 85/1769 allele-negative patients).”</td></tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td></td><td><table><tr><td>hypersensitivity reaction</td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td>ref. 2
Sousa-Pinto B et al. Pharmacogenetics of abacavir hypersensitivity: a systematic review and meta-analysis of the association with HLA-B*57:01. J Allergy Clin Immunol 2015;136:1092-4.e3.
PubMed PMID: 25934581.</td><td>3</td><td>Meta-analyses of 12 studies and 1 trial register with a total of 1234 cases with abacavir hypersensitivity and 2943 abacavir-tolerant controls. 1223 cases defined by broad clinical criteria were compared to 2869 controls (from 11 studies). 315 cases defined by strict clinical criteria were compared to 1168 controls (from 4 studies). 81 cases with patch test confirmation (immunological criteria) were compared to 1378 controls (from 4 studies).
Of the 13 studies in this meta-analysis, 9 were included in this risk analysis separately (Hetherington 2002, Mallal 2002, Hughes 2004, Martin 2004, Phillips 2005, Stekler 2006, Rodríguez-Nóvoa 2007, Mallal 2008 and Saag 2008).
Of the 13 studies in this meta-analysis, 6 were included in the meta-analysis of Tangamornsuksan 2015 (Hetherington 2002, Hughes 2004, Martin 2004, Stekler 2006, Mallal 2008 and Saag 2008).
For calculating ORs of the separate studies, a continuity correction of 0.5 or 1.0 was applied when 1 or 2 cells had a 0 count, respectively. In one of the included studies no patients had HLA-B*5701.
A random-effects meta-analysis with inverse variance weighting was used to estimate pooled ORs and respective 95% Cis.
Prospective registration of the protocol was not mentioned, but the search and selection strategy was transparent and the data extraction was standardised.
For each outcome, quality of evidence was evaluated, but quality of the included studies was not.
Publication bias analysis was not performed for the meta-analyses stratified by ethnicity. Funnel plots were shown for the stratification by case definition criteria, but not commented on.
In one of the included studies, no HLA-B*5701 positive patients were present (Munderi 2011, cases defined by broad clinical criteria, 6 cases, 241 controls). In addition, two of the included studies contained largely the same patient population (Malal 2002 (cases defined by broad clinical criteria) en Martin 2004 (cases defined by strict clinical criteria)).

Results:
<table><tr><td colspan="4">HLA-B*5701 carrier frequency in cases compared to controls:</td></tr><tr><td colspan="4">Cases defined by broad clinical criteria:</td></tr><tr><td>ethnicity</td><td>OR</td><td>95% CI</td><td>value for controls</td></tr><tr><td>all</td><td>32.1 (S)</td><td>22.2-46.4</td><td>2%</td></tr><tr><td>Whites</td><td>31.9 (S)</td><td>21.7-47.0</td><td></td></tr><tr><td>African</td><td>11.1 (S)</td><td>3.8-32.6</td><td></td></tr><tr><td>African-American</td><td>9.0 (S)</td><td>2.8-28.8</td><td></td></tr><tr><td>Latin-American</td><td>17.6 (S)</td><td>3.9-80.4</td><td></td></tr><tr><td colspan="4">No significant differences were found between ethnic groups (NS), although a trend was found for Whites versus Africans/African-Americans (p = 0.07).</td></tr><tr><td colspan="4">Cases defined by strict clinical criteria:</td></tr><tr><td>ethnicity</td><td>OR</td><td>95% CI</td><td>value for controls</td></tr><tr><td>all</td><td>177.1 (S)</td><td>48.4-652.0</td><td>2%</td></tr><tr><td colspan="4">Cases confirmed by patch testing:</td></tr><tr><td>ethnicity</td><td>OR</td><td>95% CI</td><td>value for</td></tr></table></td><td>Author’s conclusion: ”HLA-B*57:01 carriage is significantly associated with abacavir-induced hypersensitivity reactions in whites, blacks, and Hispanics, with stronger associations observed when hypersensitivity was diagnosed immunologically (patch testing) or using strict clinical criteria. On comparing studies that applied the same diagnostic criteria, no significant differences were observed between ethnic groups, confirming the hypothesis that the apparent lower sensitivity of HLA-B*57:01 in some ethnic groups mirrors a high rate of false-positive diagnoses.”</td></tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>B*5701: E</td>
<td>
<table>
<tr><td></td><td></td><td></td><td>controls</td></tr>
<tr><td>all</td><td>859.1 (S)</td><td>189.2-3901.4</td><td>3%</td></tr>
<tr><td>Whites</td><td>1,507 (S)</td><td>201-11,311</td><td></td></tr>
<tr><td>African</td><td>899.8 (S)</td><td>38.5-21,045.3</td><td></td></tr>
<tr><td colspan="4">Using patch testing (immunological criteria), the sensitivity and negative predictive value for abacavir hypersensitivity were 100% (all cases being HLA-B*5701-positive).</td></tr>
<tr><td colspan="4">For all ethnicities, the HLA-B*5701 carrier frequency in cases was 40% for broad clinical criteria, 57% for strict clinical criteria and 100% for patch test confirmation.</td></tr>
<tr><td colspan="4">For all ethnicities, the OR obtained using broad clinical criteria was significantly lower than the ORs obtained using either strict clinical criteria or patch test confirmation.</td></tr>
<tr><td colspan="4">There was substantial heterogeneity between the studies for the following comparisons:
- strict clinical criteria, all patients</td></tr>
<tr><td colspan="4">The authors did not analyse the funnel plot for publication bias. Based on 2 studies not describing the demographic characteristics of the cases and controls, they reported a serious risk of bias for the following comparisons:
- broad clinical criteria, all patients
- strict clinical criteria, all patients
- clinical criteria, African patients</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Tangamornsuksan W et al. Association of HLA-B*5701 genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. J Pharm Pharm Sci 2015;18:68-76. PubMed PMID: 25877443.</td>
<td>4

B*5701: E</td>
<td>
Meta-analyses of 9 case-control studies. 391 cases defined by clinical criteria were compared to 1618 controls (from 7 studies). 110 immunologically confirmed cases were compared to 1968 controls (from 5 studies). Patients of Asian and other ethnicity (mainly Latin-American) were only analysed in one study. Included studies scored 2 to 6 points on the 9-point Newcastle-Ottawa Quality Assessment Scale.
Of the 9 studies in this meta-analysis, 7 were included in this risk analysis separately (Hetherington 2002, Hughes 2004, Martin 2004, Stekler 2006, Zucman 2007, Mallal 2008 and Saag 2008).
A random-effects model was used for the meta-analyses. Prospective registration of the protocol was not mentioned, but the search and selection strategy was transparent and the data extraction was standardised.
Publication bias analysis was performed by funnel plot, Begg test and Egger test, but was only reported for all patients and immunologically confirmed cases.

Results:
<table>
<tr><td colspan="4">HLA-B*5701 carrier frequency in cases compared to controls:</td></tr>
<tr><td colspan="4">Cases defined by clinical criteria:</td></tr>
<tr><td>ethnicity</td><td>OR</td><td>95% CI</td><td>value for controls</td></tr>
<tr><td>all</td><td>23.6 (S)</td><td>15.4-36.3</td><td>2.2%</td></tr>
<tr><td>Whites</td><td>24.1 (S)</td><td>14.9-39.2</td><td>3.1%</td></tr>
<tr><td>African</td><td>22.8 (S)</td><td>5.6-92.7</td><td>0.6%</td></tr>
<tr><td>Asian</td><td>39.2 (S)</td><td>1.5-1000.0</td><td>0%</td></tr>
<tr><td>Latin-American</td><td>NS</td><td></td><td>0%</td></tr>
<tr><td colspan="4">Immunologically confirmed cases:</td></tr>
<tr><td>ethnicity</td><td>OR</td><td>95% CI</td><td>value for controls</td></tr>
<tr><td>all</td><td>1,056 (S)</td><td>345-3,233</td><td>2.1%</td></tr>
<tr><td>Whites</td><td>1,113 (S)</td><td>320-3,875</td><td>2.4%</td></tr>
<tr><td>African</td><td>851.6 (S)</td><td>67.9-10,682.3</td><td>2.4%</td></tr>
<tr><td colspan="4">For all ethnicities, the HLA-B*5701 carrier frequency in cases was 38% for clinical criteria and 97% for</td></tr>
</table>
</td>
<td>Author’s conclusion: ”The association between HLA-B*5701 and abacavir-induced hypersensitivity reactions is strong in the studies using immunologic confirmation to identify abacavir-induced hypersensitivity reactions.”</td>
</tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td></td><td>immunological confirmation.
There was no heterogeneity between the studies in the different comparisons.
There were no indications for publication bias.</td><td></td></tr>
<tr><td>ref. 4
Cargnin S et al. Diagnostic accuracy of HLA-B*57:01 screening for the prediction of abacavir hypersensitivity and clinical utility of the test: a meta-analytic review. Pharmacogenomics 2014;15:963-76. PubMed PMID: 24956250.</td><td>4</td><td>Meta-analyses of 17 studies comparing patients with abacavir hypersensitivity with abacavir-tolerant controls, and of 5 studies comparing HLA-B*5701-guided treatment to not HLA-B*5701-guided treatment. 920 patients with hypersensitivity defined by clinical criteria were compared to 2517 controls (from 12 studies). 146 patients with immunologically confirmed hypersensitivity were compared to 2315 controls (from 7 studies). The 5 studies investigating the utility of HLA-B*5701-guided therapy included 1434 patients with HLA-B*5701 screening and 1555 patients without HLA-B*5701 screening. In 2 studies with 950 screened and 1041 not screened patients, hypersensitivity was immunologically confirmed. In the remaining 3 studies with 484 screened and 514 not screened patients, hypersensitivity diagnoses were based on clinical criteria. The methodological quality of included studies was assessed by the QUADAS-2 tool, which consists of four key domains: patient selection, index test (i.e., HLA-B*57:01 testing), reference standard (i.e., clinically diagnosed or immunology confirmed cases), and flow and timing. The included studies consistently demonstrated a high degree of ‘applicability’, but the majority demonstrated significant methodological weaknesses with a high risk of bias for the ‘reference standard’ and ‘patient selection’.
Of the 17 studies in the meta-analysis comparing patients with and without hypersensitivity reaction, 11 were included in this risk analysis separately (Hetherington 2002, Mallal 2002, Hughes 2004, Martin 2004, Rauch 2006, Stekler 2006, Rodríguez-Nóvoa 2007, Waters 2007, Zucman 2007, Mallal 2008 and Saag 2008).
Of the 5 studies in the meta-analysis comparing HLA-B*5701-guided and not-HLA-B*5701-guided therapy, 4 were included in this risk analysis separately (Rauch 2006, Waters 2007, Zucman 2007 and Mallal 2008).
A random-effects model was used for the meta-analyses. A correction factor of 0.5 was added to all zero values.
The positive likelihood ratio is the ratio of the percentages of HLA-B*5701 carriers in patients with and without hypersensitivity. The negative likelihood ratio is the ratio of the percentages of HLA-B*5701 non-carriers in patients with and without hypersensitivity.
Prospective registration of the protocol was not mentioned, but the search and selection strategy was transparent and the data extraction was standardised.
Publication bias analysis was performed with funnel plots and Egger’s test.

Results:
HLA-B*5701 carrier frequency in patients with hypersensitivity compared to abacavir-tolerant controls:
Hypersensitivity defined by clinical criteria:
<table>
<tr><td>outcome</td><td></td><td>value for controls</td></tr>
<tr><td>OR (95% CI)</td><td>33.1 (22.3-49.0) (S)</td><td>2.0%</td></tr>
<tr><td>sensitivity</td><td>0.40</td><td></td></tr>
<tr><td>specificity</td><td>0.98</td><td></td></tr>
<tr><td>positive likelihood ratio</td><td>17.7</td><td></td></tr>
<tr><td>negative likelihood ratio</td><td>0.62</td><td></td></tr>
<tr><td colspan="3">Immunologically confirmed hypersensitivity:</td></tr>
<tr><td>outcome</td><td></td><td>value for</td></tr>
</table></td><td>Author’s conclusion: ”This meta-analysis demonstrates an excellent diagnostic accuracy of HLA-B*57:01 testing to detect immunologically confirmed abacavir hypersensitivity and corroborates existing recommendations.”</td></tr>
</table>

ref. 4, continuation	B*5701: E			
				controls
		OR (95% CI)	1141 (410-3182) (S)	2.6%
		sensitivity	0.98	
		specificity	0.97	
		positive likelihood ratio	33.8	
		negative likelihood ratio	0.073	
		Summary receiver operating characteristics curves of sensitivity and specificity indicated a good test performance (with an AUC of 92% of its maximum value for clinical criteria and 99% for immunological criteria and an Q* index (i.e. the point on the curve in which sensitivity equals specificity) of 85% of its maximum value for clinical criteria and 97% for immunological criteria).		
		For the following comparisons, the heterogeneity between the studies was high: - clinical criteria, sensitivity - immunological criteria, specificity - immunological criteria, positive likelihood ratio - clinical criteria, negative likelihood ratio For the following comparisons, the heterogeneity between the studies was significant: - clinical criteria, specificity The heterogeneity for the comparison of specificity for immunologically confirmed hypersensitivity remained high if only studies with mostly White patients were included, if only studies defining hypersensitivity as developing in the first 6 weeks of treatment were included, if only studies published after 2007 were included, and if only studies with ≥ 200 patients were included.		
		For the OR, there were no indications for publication bias.		
		Note: The authors indicate that, it turned out from their analysis that 30% (61 out of 204) of patients carrying the HLA-B*5701 allele did not develop an immunologically confirmed abacavir hypersensitivity reaction. However, the corresponding meta-analysis contains at least one case-control study (Saag 2018), so the data used by the authors are enriched for patients with a hypersensitivity reaction. This indicates that the calculated percentage is an underestimation.		
	B*5701-screening versus no screening: AA[#]	Hypersensitivity incidence in HLA-B*5701-guided therapy compared to not HLA-B*5701-guided therapy:		
		Hypersensitivity defined by either clinical or immunological criteria:		
		outcome		value for not HLA-B*5701-guided therapy
		RR (95% CI)	0.106 (0.038-0.295) (S)	5.1%
		risk difference (95% CI)	-0.050 (-0.077 - -0.023) (S)	
		Hypersensitivity defined by clinical criteria:		
		outcome		value for not HLA-B*5701-guided therapy
		RR (95% CI)	0.120 (0.027-0.525) (S)	8.0%
		risk difference (95% CI)	-0.083 (-0.144 - -0.022) (S)	

<table>
<tr><td>ref. 4, continuation</td><td></td><td>
<table>
<tr><td colspan="3">Immunologically confirmed hypersensitivity:</td></tr>
<tr><td>outcome</td><td></td><td>value for not HLA-B*5701-guided therapy</td></tr>
<tr><td>RR (95% CI)</td><td>0.061 (0.011-0.326) (S)</td><td rowspan="2">3.7%</td></tr>
<tr><td>risk difference (95% CI)</td><td>-0.034 (-0.064 - -0.005) (S)</td></tr>
<tr><td colspan="3">The calculated number to genotype in order to prevent one case of abacavir-induced sensitivity was 12 (95% CI: 7-45) for clinically diagnosed hypersensitivity, 29 (95% CI: 16-200) for immunologically confirmed hypersensitivity, and 20 (95% CI: 13-43) for clinically or immunologically diagnosed hypersensitivity. However, the heterogeneity between the studies was high.</td></tr>
<tr><td colspan="3">For the risk difference, the heterogeneity between the studies was high for all hypersensitivity criteria (clinical or immunological criteria, clinical criteria, and immunological criteria).</td></tr>
<tr><td colspan="3">There was significant publication bias for the RR, but the publication bias did not reach significance for the risk difference.</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 5
Saag M et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis 2008;46:1111-8.</td><td>4

B*5701: E</td><td>A retrospective case-control study analysed data from 130 white and 69 black patients with clinically suspected hypersensitivity reaction to abacavir (≥ 2 symptoms within 6 weeks of starting abacavir). ORs were calculated compared to the controls.
In 32% of white patients and 7% of black patients, abacavir could be confirmed immunologically as the cause of the hypersensitivity reaction through a positive skin test for abacavir.
The percentage of HLA-B*5701-positive white patients was 44% for all cases, 100% for the immunologically confirmed cases and 4% for the controls (OR 19 and 1945 respectively (S; 95% CI 8-48 and 110-34352)).
The percentage of HLA-B*5701-positive black patients was 14% for all cases, 100% for the immunologically confirmed cases and 1% for the controls (OR 17 and 900 respectively (S; 95% CI 4-164 and 38-21045)).</td><td>Authors' conclusion: "Although immunologically confirmed abacavir hypersensitivity reactions (IC ABC HSRs) are uncommon in black persons, the 100% sensitivity of HLA-B*5701 as a marker for IC ABC HSRs in both US white and black patients suggests similar implications of the association between HLA-B*5701 positivity and risk of ABC HSRs in both races."</td></tr>
<tr><td>ref. 6
Mallal S et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-79.</td><td>4

B*5701-screening versus no screening: AA#</td><td>In a double-blind, prospective, randomised study 1647 patients (84% white; HLA-B*5701 carrier prevalence 5.6%) received anti-retroviral combination therapy with abacavir for 6 weeks either following prospective HLA-B*5701 screening and exclusion of HLA-B*5701-positive patients (prospective screening group, n = 803) or without prospective screening (control group, n = 847).
Screening eliminated immunologically confirmed hypersensitivity reactions to abacavir (decrease by 100% from 2.7% to 0%; OR = 0.03 (S; 95% CI 0.00-0.18)).
Screening reduced the incidence of clinically diagnosed hypersensitivity reactions to abacavir (decrease by 56% from 7.8% to 3.4%; OR = 0.40 (S; 95% CI = 0.25-0.62)).
The percentage of HLA-B*5701-positive patients was 45.5% for the clinically diagnosed hypersensitivity reactions, 100% for the immunologically confirmed hypersensitivity reactions and 2.4% for the non-hypersensitive patients.
HLA-B*5701 had a positive predictive value of 47.9% and a negative predictive value of 100% for an immunologically confirmed hypersensitivity reaction. HLA-B*5701 had a positive predictive value of 61.2% and a negative predictive</td><td>Authors' conclusion: "HLA-B*5701 screening reduced the risk of hypersensitivity reaction to abacavir."</td></tr>
</table>

ref. 6, continuation		value of 95.5% for a clinically diagnosed hypersensitivity reaction.	
ref. 7 Waters LJ et al. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. AIDS 2007;21:2533-4.	3 B*5701-screening versus no screening: AA[#]	The incidence of hypersensitivity reactions to abacavir in a cohort (HLA-B*5701 carrier prevalence 7.3%) was determined in the year prior to (n = 144) and the year after introduction of prospective screening for HLA-B*5701 and exclusion of HLA-B*5701 positive individuals from abacavir therapy (n = 205). Exclusion of HLA-B*5701-positive patients reduced the incidence of clinically diagnosed hypersensitivity reactions from 7.5% to 2.0% (S; 73% decrease).	Authors' conclusion: "The use of prospective HLA screening reduced the incidence of abacavir hypersensitivity reactions in our cohort."
ref. 8 Rodríguez-Nóvoa S et al. Value of the HLA-B*5701 allele to predict abacavir hypersensitivity in Spaniards. AIDS Res Hum Retroviruses 2007;23:1374-6.	3 B*5701: E	A retrospective study analysed data from 53 Spanish patients (HLA-B*5701 prevalence 1-4%), 26 of whom developed a hypersensitivity reaction to abacavir and 27 patients were tolerant for abacavir. The percentage of HLA-B*5701-positive patients was elevated in the group with clinically diagnosed hypersensitivity reactions compared to the abacavir-tolerant group (42% versus 4%; S, increase of 1042%). Five of the patients with a clinically diagnosed hypersensitivity reaction to abacavir were using efavirenz or nevirapine simultaneously, which can cause similar symptoms. However, in all cases these medicines had been used without problems for more than 6 months before starting abacavir. The simultaneous presence of diseases, which can cause hypersensitivity symptoms, could not be ruled out.	Authors' conclusion: "The presence of HLA-B5701 had strong positive and negative predictive values for ABC HSR, 92% and 63%, respectively."
ref. 9 Zucman D et al. 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.	3 B*5701-screening versus no screening: AA[#]	The incidence of hypersensitivity reactions to abacavir in a cohort (HLA-B*5701 carrier prevalence 4.4%) was determined prior to (n = 49) and after the introduction of prospective scree-ning for HLA-B*5701 and exclusion of HLA-B*5701 positive individuals from abacavir therapy (n = 128). Exclusion of HLA-B*5701-positive patients from abacavir therapy reduced the incidence of suspected hypersensitivity reactions from 22.5% to 0.8% (S; 96% decrease). The incidence of actual hypersensitivity reactions (i.e. following exclusion of patients for whom a different cause could be determined for the reaction) decreased from 12% to 0% (significance not determined; decrease by 100%). In addition, there was a decrease in the percentage of patients that had to stop abacavir due to symptoms other than hypersensitivity (from 10.2% to 0.73%; S; 93% decrease).	Authors' conclusion: "In our ethnically mixed population, prospective HLA-B*5701 testing resulted in an absence of the occurrence of hypersensitivity and reduced the rate of unwarranted interruptions of abacavir therapy."
ref. 10 Rauch A et al. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. Clin Infect Dis 2006;43:99-102.	4 B*5701-screening versus no screening: AA[#]	The incidence of hypersensitivity reactions to abacavir in a cohort (HLA-B*5701 carrier prevalence 7.7%) was determined prior to (n = 199) and after the introduction of prospective screening for HLA-B*5701 and exclusion of HLA-B*5701 positive individuals from abacavir therapy (n = 151, of whom 3x HLA-B*5701 positive). Prospective screening for HLA-B*5701 reduced the incidence of hypersensitivity reactions to abacavir from 8% to 2.0% (S; 75% decrease). The 3 (immunologically confirmed) hypersensitivity reactions following prospective screening occurred in the 3 HLA-B*5701-positive patients who were treated with abacavir before the result of the screening was known (n = 2), or because absence of additional risk factors was suspected (n = 1). No hypersensitivity reaction occurred in the 148 HLA-B*5701-negative patients. The percentage of patients that had to stop abacavir due to symptoms other than hypersensitivity decreased following	Authors' conclusion: "In this prospective study, involving 260 abacavir-naïve individuals (7.7% of whom were positive for HLA-B*5701), we confirm the usefulness of genetic risk stratification, with no cases of abacavir hypersensitivity among 148 HLA-B*5701-negative recipients."

ref. 10, continuation		the introduction of prospective screening, but this was not significant.	
ref. 11 Stekler J et al. Abacavir hypersensitivity reaction in primary HIV infection. AIDS 2006;20:1269-74.	3 B*5701: E	A prospective case-control study analysed data from 9 patients with primary HIV infection and a clinically diagnosed hypersensitivity reaction to abacavir. The presence of HLA-B*5701 was associated with an increased risk of hypersensitivity reactions to abacavir (RR = 6.9 (S; 95% CI 3.5-13.6); percentage HLA-B*5701-positive patients 22% for the cases versus 0% for the controls).	Authors' conclusion: "As in chronic infection, HLA-B*5701 is associated with the abacavir hypersensitivity reaction in primary HIV infection."
ref. 12 Phillips EJ et al. Clinical and immunogenetic correlates of abacavir hypersensitivity. AIDS 2005;19:979-81.	4 B*5701: E	A case-control study analysed data from 7 patients with an immunologically confirmed hypersensitivity reaction to abacavir and 11 controls. The percentage of HLA-B*5701-positive patients was higher in the cases than in the controls (100% versus 9%; S).	
ref. 13 Hughes DA et al. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. Pharmacogenetics 2004;14:335-42.	4 B*5701: E	A case-control study analysed data from 13 patients with a clinically diagnosed hypersensitivity reaction to abacavir. Co-medication was ruled out as the cause of the hypersensitivity reaction by re-challenge with the other medicines that were started simultaneously with abacavir. The percentage of HLA-B*5701-positive patients was higher in the cases than in the controls (46% versus 10%; OR = 7.9 (S; 95% CI 1.5-41.4)). After pooling of the data with data from two previously published studies (Mallal et al. and Hetherington et al., 2002), the percentages were 51% versus 4% and the OR was 29 (S; 95% CI 6.4-132.3).	Authors' conclusion: "Abacavir hypersensitivity is associated with HLA B*5701, and pre-prescription pharmacogenetic testing for this appears to be a cost-effective use of healthcare resources."
ref. 14 Martin AM et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. Proc Natl Acad Sci U S A 2004;101:4180-5.	4 B*5701: E	In this study, the data from the cohort described in Mallal et al., 2002 are analysed in more detail, following expansion with data from 48 additional patients, 2 of whom had a hypersensitivity reaction to abacavir. The 48 additional patients were also included in the study by Rauch, 2006. Fine mapping of the locus that was found demonstrated that - of the genes in this locus - HLA-B*5701 is most strongly associated with hypersensitivity to abacavir. The gene is present in 94.4% of the cases and 1.7% of the controls (OR = 960 (S; 95% CI not stated)). Of the 18 clinically diagnosed hypersensitivity reactions in the old study, 3 were the result of co-medication (negative skin test). One case that was incorrectly classified as "hypersensitivity not ruled out" was actually a hypersensitivity reaction (hypersensitivity reaction disappeared again spontaneously, apparently through desensitisation). As a result of these new data, the number of patients with a hypersensitivity reaction in the old study decreased to 16.	Authors' conclusion: "These data indicate that the concurrence of HLA-B*5701 and Hsp70-Hom M493T alleles is necessary for the development of abacavir hypersensitivity."
ref. 15 Hughes AR et al. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations. Pharmacogenomics 2004;5:203-11.	3	This is a continuation study of the study by Hetherington et al., 2002. A retrospective case-control study analysed data from 277 patients with a clinically diagnosed hypersensitivity reaction to abacavir and 265 controls. The cases were divided into 189 white (including 31 women), 51 Hispanic and 37 black. A total of 125 of the cases met the restrictive diagnostic criteria for the hypersensitivity reaction to abacavir (ruling out diagnosis "possible hypersensitivity reaction to abacavir" and ruling out use of efavirenz and nevirapine). Out of the genes on the locus that was found, HLA-B*5701 is most strongly associated with hypersensitivity to abacavir.	Authors' conclusion: "HLA-B*5701 alone lacks sufficient predictive value to identify patients at risk for hypersensitivity to abacavir across diverse patient populations."

ref. 15, continuation	B*5701: E	- For the following groups, the percentage of HLA-B*5701-positive patients was significantly higher in the cases than in the controls: % HLA-B*5701 in cases / % HLA-B*5701 in controls / OR whites, standard diagnosis: 48 / 4 / 21.4 white males, standard diagnosis: 46 / 4 / 19.3 white females, standard diagnosis: 59 / 4 / 36.8 Hispanics, standard diagnosis: 22 / 0 / 30.4 whites, restrictive diagnosis: 61 / 4 / 35.7 white males, restrictive diagnosis: 57 / 4 / 29.0 white females, restrictive diagnosis: 85 / 4 / 143 Hispanics, restrictive diagnosis: 20 / 0 / 29.2 - For the following groups, the percentage of HLA-B*5701-positive patients was not significantly higher in the cases than in the controls: % HLA-B*5701 in cases / % HLA-B*5701 in controls / OR blacks, standard diagnosis: 8 / 2 / 3.5 blacks, restrictive diagnosis: 16 / 2 / 7.5	
ref. 16 Hetherington S et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359:1121-2.	3 B*5701: E	A retrospective case-control study analysed data from 84 patients with a clinically diagnosed hypersensitivity reaction to abacavir and 113 controls. No control was found for 41% of the cases. A total of 77% of the cases were white. Out of the genes in the HLA-B region, HLA-B*57 is most strongly associated with hypersensitivity to abacavir. The association was particularly clear for the white sub-group: % HLA-B*5701 in cases / % HLA-B*5701 in controls whites: 55 / 1 blacks: 0 / 0 others: 10 / 0 Of the 8 cases where the hypersensitivity to abacavir was confirmed by re-challenge, 75% were HLA-B57-positive. The results were similar, whether matching of controls was included in the analysis or not.	Authors' conclusion: "Given the limitations noted, we believe that recommendation of HLA-B57 testing as a screening tool is premature."
ref. 17 Mallal S et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir.	3 B*5701: E	In a cohort of 200 primarily White patients being treated with abacavir, 18 patients (9%) developed a clinically diag-nosed hypersensitivity reaction to abacavir, 15 patients did not meet the diagnostic criteria and the remaining 167 patients were abacavir-tolerant. HLA-B*5701 was present in 78% of the abacavir hypersensitive patients and 2% of the tolerant patients (OR = 117 (S; 95% CI 29-481)).	Authors' conclusion: "In our population, withholding abacavir in those with HLA-B*5701, HLA-DR7, and HLA-DQ3 should reduce the prevalence of hypersensitivity from 9% to 2·5%."

Lancet 2002;359:727-32.			
ref. 18 SmPC Ziagen (abacavir) 28-07-20.	0 B*5701: F	Therapeutic indications: Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele. Boxed warning: Hypersensitivity reactions Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately. The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele. Therefore the following should be adhered to: • HLA-B*5701 status must always be documented prior to initiating therapy. • Ziagen should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen. (e.g. Kivexa, Trizivir, Triumeq) • Ziagen must be stopped without delay, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Ziagen after the onset of hypersensitivity may result in a life-threatening reaction. • After stopping treatment with Ziagen for reasons of a suspected HSR, Ziagen or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir, Triumeq) must never be reinitiated. • Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death. • In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Ziagen tablets *Clinical description of abacavir HSR* Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Almost all HSR to abacavir include fever and/or rash. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.	

ref. 18, continuation		Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re-initiating abacavir therapy. Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.	
ref. 19 SmPC Ziagen (abacavir), USA, 24-11-20.	0 B*5701: F	<u>Boxed warning</u>: Hypersensitivity reactions Serious and sometimes fatal hypersensitivity reactions have occurred with Ziagen (abacavir). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele. Ziagen is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with Ziagen or reinitiation of therapy with Ziagen, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue Ziagen immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to Ziagen, NEVER restart Ziagen or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity. <u>Dose and administration</u>: Screen for the HLA-B*5701 allele prior to initiating therapy with Ziagen. <u>Contraindications</u>: Ziagen is contraindicated in patients who have the HLA-B*5701 allele. <u>Warnings</u>: Hypersensitivity reactions Serious and sometimes fatal hypersensitivity reactions have occurred with Ziagen (abacavir). These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with Ziagen (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment. Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making. Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with Ziagen: • All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with Ziagen or reinitiation of therapy with Ziagen, unless patients have a previously documented HLA-B*5701 allele assessment.	

ref. 19, continuation		• Ziagen is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. • Before starting Ziagen, review medical history for prior exposure to any abacavir-containing product. NEVER restart Ziagen or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status. • To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue Ziagen immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). • If a hypersensitivity reaction cannot be ruled out, do not restart Ziagen or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death, can occur within hours. • If a hypersensitivity reaction is ruled out, patients may restart Ziagen. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of Ziagen or any other abacavir-containing product is recommended only if medical care can be readily accessed. • A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.	

Risk group	-

Comments:

- The working group considers Mallal 2008 to be the most important article.
- For the period after July 2008 only studies with more than 500 patients were included. Other studies did not add enough to the evidence. The meta-analysis of Hu 2019 (Hu K et al. Associations between human leukocyte antigen polymorphisms and hypersensitivity to antiretroviral therapy in patients with human immunodeficiency virus: a meta-analysis. BMC Infect Dis. 2019;19:583. PMID: 31277607) was not included, because only 3 of the 17 studies in this meta-analysis concerned abacavir. In addition, only the effect of HLA-B*57 was investigated, not the effect of HLA-B*5701.
- Existing guideline:
  - Martin MA et al. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing: 2014 update. Clin Pharmacol Ther 2014;95:499-500. PubMed PMID: 24561393 and Martin MA et al. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing. Clin Pharmacol Ther 2012;91:734-8. PubMed PMID: 22378157.
    CPIC indicates that there is substantial evidence linking the presence of the HLA-B*5701 genotype with abacavir hypersensitivity and that the evidence is of high quality in the majority of cases. As references reporting the initial association in predominantly white males, they mention Mallal 2002 and Hetherington 2002, with Hughes 2004 replicating this association. As references showing that prospective screening and excluding HLA-B*5701-positive patients from starting abacavir significantly reduces the incidence of hypersensitivity reactions, they mention Rauch 2006, Waters 2007 and Zucman 2007. In addition, CPIC indicates that the latter studies, along with Saag 2008 found that HLA-B*5701 was also predictive of hypersensitivity reactions in females and in African Americans. CPIC mentions Mallal 2008 because it showed that genetic prescreening for HLA-B*5701 resulted in no immunologically confirmed hypersensitivity reactions among HLA-B*5701-negative patients in the genetic testing arm, versus a 2.7% incidence of immunologically confirmed hypersensitivity reactions among 842 unscreened patients in the standard-of-care control arm. CPIC indicates that the results of Mallal 2008 and the existing body of evidence prompted the FDA to implement a black box warning in 2008 about the high risk of HLA-B*5701-associated hypersensitivity reactions. The FDA recommended that all patients be screened before being treated with abacavir (including those who had previously tolerated the drug and were being restarted on the therapy) and that abacavir not be initiated in carriers of HLA-B*5701. All the key references mentioned above are included in our risk analysis. Based on these and other references, CPIC indicates that abacavir is not recommended in carriers of HLA-

B*5701. CPIC classifies this recommendation as strong, meaning that the evidence is high quality and the desirable effects clearly outweigh the undesirable effects. In the full text of the guideline, CPIC expands this recommendation by stating that in abacavir-naive individuals who are HLA-B*5701-positive, abacavir should be considered only under exceptional circumstances when the potential benefit, based on resistance patterns and treatment history, outweighs the risk.
The therapeutic recommendations for abacavir are indicated below:

Recommended therapeutic use of abacavir in relation to HLA -B genotype		
Genotype	Recommendation	Classification of recommendation
Carrier of HLA-B*5701	Abacavir is not recommended.	Strong
Non-carrier of HLA-B*5701	Use abacavir per standard dosing guidelines.	Strong

As evidence linking HLA-B*5701 genotype with abacavir phenotype, CPIC mentions Schnyder 2013, Almeida 2008, Chessman 2008, Mallal 2008, Rauch 2008, Saag 2008, Young 2008, Rodríguez-Nóvoa 2007, Waters 2007, Zucman 2007, Rauch 2006, Stekler 2006, Phillips 2005, Hughes 2004 Pharmacogenetics, Hughes 2004 Pharmacogenomics, Martin 2004, Hetherington 2002, Mallal 2002 and Phillips 2002. All but 6 of these studies are included in our risk analysis. Almeida 2008 and Chessman 2008 are not included in our risk analysis, because they only contain in vitro data, and Rauch 2008 is not included, because it investigates less than 500 patients, Young 2008 is not included in our risk analysis, because it does not specify a non-screening control cohort. For this reason, its value only relies on the investigation of an USA cohort and it does not add enough information for health care professionals treating Dutch or European patients to be included. Schnyder 2013 and Phillips 2002 are not included in our risk analysis, because they only provide data on skin patch testing and the longevity of the immune response after patients developed hypersensitivity. Because rechallenge with abacavir is contraindicated after hypersensitivity development, the applicability of these data is insufficient. In addition, our risk analysis includes the meta-analyses of Sousa-Pinto 2015, Tangamornsuksan 2015 and Cargnin 2014. CPIC indicates that the studies included in the guideline provide a high level of evidence that the presence of HLA-B*5701 is predictive of clinically diagnosed abacavir hypersensitivity (based on 10 references including Rauch 2008) and of immunologically confirmed (patch test) hypersensitivity (Mallal 2008, Saag 2008 and Philips 2005). In addition, CPIC indicates that these studies provide a high level of evidence that prospective screening of HLA-B*5701 reduces the incidence of clinically diagnosed abacavir hypersensitivity (based on 5 references including Young 2008) and of immunologically confirmed (patch test) hypersensitivity (Mallal 2008, Young 2008 and Rauch 2006). Finally, CPIC indicates a high level of evidence that abacavir skin patch testing results correlate strongly with the presence of HLA-B*5701 and can still be reactive years after original presentation of abacavir hypersensitivity, indicating a durable immune response (Schnyder 2013, Phillips 2005 and Phillips 2002).

Pre-emptive genotyping

Concerning pre-emptive genotyping, CPIC indicates that they agree with five other guidelines, including the 2011 publication of the KNMP Pharmacogenetics Working Group, that HLA-B*5701 screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy. This is consistent with the recommendations of the FDA, the US Department of Health and Human Services, and the European Medicines Agency. In addition, CPIC indicates that in abacavir-naive individuals who are HLA-B*5701-positive, abacavir is not recommended and should be considered only under exceptional circumstances when the potential benefit, based on resistance patterns and treatment history, outweighs the risk. CPIC mentions that where HLA-B*5701 genotyping is not clinically available (such as in resource-limited settings), some have advocated initiating abacavir, provided there is appropriate clinical monitoring and patient counselling about the signs and symptoms of hypersensitivity reactions although this remains at the clinician's discretion.

CPIC indicates that there is some debate among clinicians regarding whether HLA-B*5701 testing is necessary in patients who had previously tolerated abacavir chronically, discontinued its use for reasons other than hypersensitivity reactions, and are now planning to resume abacavir. The presence of HLA-B*5701 has a positive predictive value of ~50% for immunologically confirmed hypersensitivity (Mallal 2008), indicating that some HLA-B*5701-positive individuals can be, and have been, safely treated with abacavir. However, CPIC was unable to find any data to show that HLA-B*5701-positive individuals with previous, safe exposure to abacavir had zero risk of hypersensitivity reactions upon re-exposure. Although there are isolated case reports of previously asymptomatic patients developing a hypersensitivity-like reaction after restarting abacavir, there were confounding circumstances (Loeliger AE et al. The abacavir hypersensitivity reaction and interruptions in therapy. AIDS 2001;15:1325-6; Frissen PH et al. Severe anaphylactic shock after rechallenge with abacavir without preceding hypersensitivity. AIDS 2001;15:289; and Sahly HME. Development of abacavir hypersensitivity reaction after rechallenge in a previously asymptomatic patient. AIDS 2004;18:359-60). Many of the patients had complicating concomitant illnesses that could have masked an hypersensitivity reaction during initial abacavir therapy, and none were immunologically confirmed, making the case reports difficult to interpret. Furthermore, most of these case reports precede the availability of HLA-B*5701 genetic testing, making it impossible to determine from the published data whether there could be a risk of a hypersensitivity reaction upon re-exposure to abacavir in previously asymptomatic HLA-B*5701-positive patients. In addition, CPIC indicates that there may also exist a small group of patients who

have been on chronic abacavir therapy since before the introduction of HLA-B*5701 genotyping. Given that virtually all abacavir hypersensitivity reactions occur within the first several weeks of therapy, and that ~50% of HLA-B*5701 carriers can safely take abacavir, CPIC was unable to find any evidence to suggest that HLA-B*5701-positive individuals on current, long-term, uninterrupted abacavir therapy are at risk of developing hypersensitivity reactions. CPIC mentions that existing clinical guidelines, including the 2011 publication of the KNMP Pharmacogenetics Working Group, have a blanket recommendation that all HLA-B*5701-positive individuals should avoid abacavir, regardless of patient history. Although HLA-B*5701 genotyping has proven utility in significantly reducing the incidence of both clinically diagnosed and immunologically confirmed hypersensitivity in patients being newly considered for abacavir therapy (Martin 2004, Rauch 2006, Waters 2007, Mallal 2008 and Young B et al. First large, multicenter, open-label study utilizing HLA-B*5701 screening for abacavir hypersensitivity in North America. AIDS 2008;22:1673-5), CPIC indicates that the connection between HLA-B*5701 genotype and risk of hypersensitivity reactions in patients with previous asymptomatic abacavir use is less clear.
On 6-12-2022, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

- Cost-effectiveness:

QALY is quality-adjusted life-year

- Morris SA et al. Cost Effectiveness of pharmacogenetic testing for drugs with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines: a systematic review. Clin Pharmacol Ther 2022 Sep 23 (online ahead of print). PMID: 36149409.
  In a systematic review, 8 cost-effectiveness studies for HLA-B*5701 and abacavir were identified: Goh 2019; Ruiz-Iruela 2016; Kapoor 2015; Kauf 2010; Nieves Calatrava D et al. Cost-effectiveness analysis of HLA-B*5701 typing in the prevention of hypersensitivity to abacavir in HIV+ patients in Spain. Enferm Infecc Microbiol Clin 2010;28:590-5. PubMed PMID: 20144493; Wolf 2010; Schackman 2008; and Hughes 2004).
  2 of the studies indicated that genotype-guided therapy is cost-saving (Kauf 2010 and Wolf 2010), 4 that it is cost-effective (Ruiz-Iruela 2016, Nieves Calatrava 2010, Schackman 2008, and Hughes 2004), 1 that it is not-cost-effective (Kapoor 2015), and 1 that it is uncertain (i.e. found to be dependent upon one or more parameters in the model (e.g., event rate, sample size, allele frequency, cost of the drug and/or event of interest)) (Goh 2019).
  Only one of these studies had a Quality of Health Economic Studies (QHES) score < 75, suggesting no high quality (Goh 2019, score 67). The other 7 had scores ranging from 87 to 100.
  4 studies were performed in Europe (Ruiz-Iruela 2016, Nieves Calatrava 2010, Wolf 2010, and Hughes 2004), 2 in North America (Kauf 2010 and Schackman 2008, and 2 in Asia (Goh 2019 and Kapoor 2015).
  2 of the studies did not report the costs per hypersensitivity reaction avoided or per quality-adjusted life-year gained (Goh 2019 and Wolf 2010), with Goh 2019 indicating that this varied depending on early-stage versus late-stage and population.
- Manson LEN et al. Genotyping for HLA risk alleles to prevent drug hypersensitivity reactions: impact analysis. Pharmaceuticals (Basel) 2021;15:4. PMID: 35056062.
  Genotyping HLA-B*5701 in Dutch abacavir initiators has a number needed to genotype of 31 to prevent one case of abacavir hypersensitivity and is cost-saving. Genotype-guided therapy is € 39 per patient cheaper than not genotype-guided therapy. Nationwide implementation can potentially prevent 28 cases of abacavir hypersensitivity each year in the Netherlands (873 first prescriptions of abacavir per year). This would save The Netherlands the limited amount of € 34,000 each year.
  Prevalence of HLA-B*5701 carriers in the Dutch population (6.6%) was derived from the Allele Frequency Net Database and literature. The probability of abacavir-induced hypersensitivity reaction in patients testing positive for HLA-B*5701 (48%) was derived from the DPWG guideline for HLA-B*5701 and abacavir. The mortality rate of abacavir hypersensitivity reaction (0.07%) was derived from literature. The calculation was further based on cost of abacavir-based ART treatment (dolutegravir/abacavir/lamivudine) of € 29.62/day, cost of alternative, non-abacavir-based ART treatment (bictegravir/emtricabine/tenofoviralafenamide) of € 29.54/day, cost of abacavir hypersensitivity reaction (cost of “intensive treatment for allergy”) of € 3700, and cost of the HLA-B*5701 genotyping test of € 79.
- Zhou Y et al. Global frequencies of clinically important HLA alleles and their implications for the cost-effectiveness of pre-emptive pharmacogenetic testing. Clin Pharmacol Ther 2021;109:160-74. PMID: 32535895.
  The authors consolidated HLA genotypes of 3,586,065 individuals from 56 countries provided by the Allele Frequency Net Database and the Estonian Biobank. and modelled the country-specific cost-effectiveness of genetic testing. They conclude that at incremental cost-effectiveness ratio thresholds of US$40,000, testing of HLA-B*5701 in patients initiating abacavir was cost-effective in the majority of countries with potential exceptions of East Asia, Saudi Arabia, Ghana, and Zimbabwe. Incremental cost thresholds for HLA-B*5701 genotyping were positive across South Asia, Europe, and the Americas. Using the United States as an example, the values indicate that pre-emptive genotyping is cost-effective until the increase in cost of the alternative ART per patient exceeds US$2,419.80 for a “willingness-to-pay” threshold of US$40,000 (US$ 979.80–US$5,299.80 for US$10,000 to US$100,000, respectively). Furthermore, pre-emptive genotyping is cost-saving in the United States if the increase in treatment costs of the alternative ART is < US$499.80. Monthly costs for first-line abacavir-based therapy (abacavir, lamivudine, and efavirenz) in the United States were US$1,135, whereas costs of the alternative tenofovir, emtricitabine, and efavirenz treatment regimen

were only slightly higher at US$1,139. Based on the average life expectancy of patients initiating abacavir treatment, the incremental cost of switching from abacavir-based regimens to non-abacavir containing regimens is US$1,485 and, thus, well below the value of US$2,419.80, which corroborates the cost-effectiveness of HLA-B*5701 testing prior to the initiation of abacavir therapy in the United States. In contrast, incremental cost thresholds are negative in East Asia and several countries in Africa and West Asia, including Mali, Ghana, Saudi Arabia, China, Japan, and South Korea, which suggests that the cost of the alternative ART would have to be cheaper than abacavir-based therapy for pre-emptive genotyping in these countries to be cost-effective. These effects are primarily attributed to the low frequency of HLA-B*5701 in these populations and the corresponding substantial increase in patients who need to be genotyped to prevent one hypersensitivity reaction. As such, these countries could benefit most from reduced genotyping costs.

Abacavir-based ART for all was compared with genotype-guided therapy, consisting of ART without abacavir for HLA-B*5701 positive patients and abacavir-based ART for HLA-B*5701 negative patients. Based on robust clinical trial data the authors considered abacavir-containing treatment regimens as therapeutically equivalent to regimens without abacavir.

In case of countries with heterogeneous population structures, the authors aggregated subpopulation-specific HLA-B*5701 frequency information based on the national population composition. For countries with no available information on allele frequency, they used the averaged continental allele frequency to calculate the number of carriers per continent.

The authors reported the highest HLA-B*5701 frequency in Sri Lanka (9.3%), India (6.2%), and the Indian diaspora in South Africa (10.2%) and the lowest in South Korea, Japan, and Saudi Arabia (< 0.3%) and in Mali and South African Zulus (0%). Furthermore, frequencies were high in Western Europe, ranging from 2% in Belgium to 5.8% in Ireland, whereas its prevalence was lower in Scandinavia (1% in Sweden and 1.7% in Finland) and the Eastern Mediterranean coast (1.5% in Turkey and 1.6% in Greece).

Direct medical costs were calculated. The calculation was based on the average price of treatment of abacavir hypersensitivity reaction reported in literature of US$2547 and genotyping costs of US$40. Due to a strong variation of drug prizes across the world, drug prizes were not included, but the total cost by which the alternative treatment can exceed the cost of allopurinol for the genotype-guided strategy to be cost-effective were calculated. Positive and negative predictive values for abacavir hypersensitivity development and HLA-B*5701 (47.9% and 100% respectively) were obtained from literature (Mallal 2008).

When genotyping costs of US$141 instead of US$40 were used in the calculations, genotype-guided therapy remained cost-effective for Europe and the United States, but became cost-ineffective throughout most of Asia and Africa.

- Plumpton CO et al. Cost-effectiveness of panel tests for multiple pharmacogenes associated with adverse drug reactions: an evaluation framework. Clin Pharmacol Ther 2019;105:1429-38. PubMed PMID: 30466189.

  Genotyping British HIV patients eligible for abacavir with a £50 multigene panel for HLA-B*5701, HLA-A*3101, HLA-B*1502, HLA-B*5801, HLA-B (158T), and HLA-DQB1 (126Q), was cost-effective with a probability of 1.0 at a threshold of £30,000 per quality adjusted life year (QALY) gained. Testing was cost-saving, resulting in a gain of 0.0170 QALY and a cost reduction of −£3,098.

  The calculation was from a health-care payer perspective. Calculation for a single gene panel (only HLA-B*5701) was based on Kauf 2010 and testing costs were assumed to be independent of the number of genes tested.

- Goh KS et al. HLA-B*5701 genotyping for abacavir prescription: re-examination of its cost-effectiveness in Singapore. Ann Acad Med Singap 2019;48:133-8. PMID: 31131386.

  The calculations in Kapoor 2015 were repeated with new information on HLA-B*5701 genotyping based on hospital data, including 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. The new calculations 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, 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, indicating that genotype-guided therapy is both better and cheaper in these patients.

  For Han Chinese, Malays, and Indian patients the HLA-B*5701 carrier frequencies were 0.26%, 2.44%, and 15.1% respectively. Distinction between patients for whom tenofovir is contraindicated and patients who could be prescribed both abacavir and tenofovir was maintained. Usage of zidovudine-based ART in patients in which neither tenofovir nor abacavir was an option, was also maintained. The distinction between late-stage and early-stage HIV infection and the threshold of US$50.000 per quality-adjusted life-year gained were also maintained. 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.

  For Chinese patients with early-stage HIV, HLA-B*5701 genotyping is found to increase quality adjusted

life-years (QALYs) by 0.000014 for an incremental cost of US$ 208 compared with the strategy with no genotyping. This corresponds to additional costs of US$ 15,305,250/QALY gained. The corresponding costs for late-stage Chinese patients were US$ 23,361,205/QALY, for Malay early-stage HIV patients US$ 8,061,323/QALY and for Indian early-stage HIV patients US$ 7,336,974/QALY. For Malay and Indian late-stage HIV patients, genotype-guided therapy delivered more QALYs and costs less than abacavir-based therapy for all, i.e. was cost-saving. The calculation was based on average monthly cost of abacavir + lamivudine of US$ 92, average monthly cost of tenofovir + lamivudine of US$ 319, average monthly cost of zidovudine + lamivudine of US$ 372, average monthly cost of efavirenz of US$ 85, average monthly cost of hypothetical drug of US$ 740, costs of three clinician consultation for side effects of US$ 210, costs of treating abacavir hypersensitivity cases of US$ 1983, costs of treating other intolerable side effects of abacavir of US$ 1918, costs involved in fatal abacavir hypersensitivity cases of US$ 31,600 (not changed), costs of treating intolerable side effects of tenofovir of US$ 3499, costs of treating intolerable side effects of zidovudine of US$ 3490, costs of routine renal panel and urine analysis of US$ 47, and a genetic test price of US$ 110.

- Verbelen M et al. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? Pharmacogenomics J 2017;17:395-402. PMID: 28607506.
  In a literature review, 5 economic evaluations for HLA-B*5701 and abacavir were identified: Kapoor 2015; Kauf 2010; Nieves Calatrava D et al. Cost-effectiveness analysis of HLA-B*5701 typing in the prevention of hypersensitivity to abacavir in HIV+ patients in Spain. Enferm Infecc Microbiol Clin 2010;28:590-5. PubMed PMID: 20144493; Schackman 2008; and Hughes 2004).
  The majority (4 out of 5) of these economic evaluations concluded in favour of HLA-B*5701 testing (all except Kapoor 2015), with 2 indicating that genotype-guided therapy is cost-saving (Kauf 2010 and Hughes 2004). In case the HLA-B*5701 status of the patients would be known already, 3 out of 5 economic evaluations would indicate genotype-guided therapy to be cost-saving, 1 would indicate it to be cost-effective and the cost-effectiveness in this case could not be determined for the fifth evaluation.
  2 studies were performed in Europe (Nieves Calatrava 2010 and Hughes 2004), 2 in the USA (Kauf 2010 and Schackman 2008), and 1 in Asia (Kapoor 2015).
  2 of the studies reported the costs per adverse reaction avoided instead of per quality-adjusted life-year gained (cost-effectiveness analyses instead of cost utility analyses) (Nieves Calatrava 2010 and Hughes 2004).
- Ruiz-Iruela C et al. HLA-B*57:01 genotyping in the prevention of hypersensitivity to abacavir: 5 years of experience. Pharmacogenet Genomics 2016;26:390-6. PubMed PMID: 27195528.
  In Spanish patients treated with abacavir in a tertiary care hospital, systematic HLA-B*5701 genotyping represented additional costs of € 306 per clinically diagnosed hypersensitivity reaction avoided. In the sensitivity analysis, pharmacological therapy cost was the major influencing factor found in the estimation of the 'costs per hypersensitivity reaction avoided'. In modelling, the costs decreased with an increase in HLA-B*5701 prevalence and vice-versa. In terms of clinical utility, the incidence ratio was 0.040 (95% confidence interval 0.0009–0.2399) and statistically significant differences were found between both groups ($P = 1.40\times10^{-7}$).
  The authors indicate that they confirmed the cost-effectiveness of systematic genotyping in candidate patients for abacavir therapy. The savings associated with the prescription of the cheaper abacavir/lamivudine therapy instead of tenofovir/emtricitabine were greater than the costs associated with HLA-B*5701 testing. In addition, they indicate that they have shown that cost-effectiveness is a dynamic parameter closely linked to allele prevalence and pharmacological therapy costs.
  The calculation was based on a retrospective study with two cohorts including 780 and 473 patients before and after implementation of systematic HLA-B*5701 genotyping before abacavir treatment. Hypersensitivity reaction to abacavir was defined as the occurrence of general symptoms such as fever, nausea, diarrhoea, or rash in patients who discontinued abacavir during the initial 6 weeks of therapy. The syndrome should have been completely resolved after abacavir cessation. Immunological confirmation was not performed.
  Before implementation of systematic HLA-B*5701 genotyping, all patients were treated with abacavir-based therapy. After implementation of systematic HLA-B*5701 genotyping, HLA-B*5701-negative patients were treated with abacavir-based therapy and HLA-B*5701-positive patients with tenofovir-based therapy.
  The costs of drug treatment during the first 6 months, the costs of the genotyping test, and the direct healthcare costs of treating hypersensitivity reactions were included in the calculation. The incidence of abacavir hypersensitivity reactions was 5% (39 of the 780 patients) before implementation of systematic HLA-B*5701 genotyping and 0.2% (1 of the 473 patients) thereafter. One HLA-B*5701-positive patient developing abacavir hypersensitivity reaction after implementation of systematic HLA-B*5701 genotyping, because of receiving abacavir before performance of the genotyping test, was excluded from the calculation. The HLA-B*5701 carrier frequency in the population was 5.4%. Systematic genotyping avoided 47.9 hypersensitivity reactions/1000 patients screened, which supposes an incremental cost of € 15,000 (€ 2079/patient/6 months in the first cohort vs. € 2094/patient/6 months in the second cohort). The calculation showed an additional cost of € 306 per hypersensitivity reaction avoided. The calculation was based on costs for management of one hypersensitivity reaction of € 200.20, costs of Kivexa (abacavir + lamivudine) of € 342 per month, costs of Truvada (tenofovir + emtricitabine) of € 417 per month, and genotyping costs of € 17.89.

Variation of input data found the additional costs per hypersensitivity reaction avoided, to be most influenced by the costs of tenofovir/emtricitabine and abacavir/lamivudine (increase per 1% treatment cost increase with 2.75% and −2.25%, respectively). The influence of the costs of the genetic test and the hypersensitivity treatment was smaller (increase per 1% test/treatment cost increase with 1.09% and −0.59%, respectively).

- Plumpton CO et al. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. Pharmacoeconomics 2016;34:771-93. PubMed PMID: 26984520.
  The authors performed a systematic literature review of economic evaluations of pharmacogenetic tests of HLA-B*5701 prior to prescription of abacavir. The authors conclude that evidence exists to support the cost-effectiveness of genotyping prior to abacavir with the majority of high quality studies indicating that genotyping was either better and cheaper, cost-saving or cost-effective across a variety of populations. The implication for clinicians and policy makers is that testing of HLA-B*5701 prior to start of abacavir should be considered for adoption as routine practice.
  Six economic evaluations were retrieved: three conducted in Europe (Hughes 2004, Wolf 2010 and Nieves Calatrava D et al. Cost-effectiveness analysis of HLA-B*5701 typing in the prevention of hypersensitivity to abacavir in HIV+ patients in Spain. Enferm Infecc Microbiol Clin 2010;28:590-5. PubMed PMID: 20144493), two conducted in the USA (Schackman 2008 and Kauf 2010), and one in Singapore (Kapoor 2015). Three evaluations were cost-utility analyses (Schackman 2008, Kauf 2010 and Kapoor 2015). Three were (also) cost-effectiveness analyses reporting events averted (Hughes 2004, Kauf 2010 and Nieves Calatrava 2010). One study was a cost-minimisation or cost-benefit analysis (Wolf 2010). Costs were calculated from the perspective of the healthcare provider in four studies (Hughes 2004, Kauf 2010, Wolf 2010 and Nieves Calatrava 2010) and from a societal perspective in one (Wolf 2010).The quality of reporting in the economic evaluations was high for all studies. High quality was defined as reporting of more than 85% of items on a 24-item checklist for economic health evaluations. The perspective was unclear in Kapoor 2015, that also did not specify that costs and outcomes were discounted. Hughes 2004 stated that the evidence supporting the effectiveness of pharmacogenetics was retrieved from cohort studies. Four studies used random controlled trial evidence of the effectiveness of pharmacogenetics testing (Schackman 2008, Wolf 2010, Nieves Calatrava 2010 and Kapoor 2015). Kauf 2010 mentioned trials and randomised studies, but referred to genetic sub-studies of trials that were primarily designed for other purposes as source for the evidence. The majority of studies indicated that testing was either both cheaper and better (Hughes 2004, Schackman 2008, Kauf 2010, Wolf 2010) or cost effective (Hughes 2004 for didanosine and tenofovir as alternative treatment and Nieves Calatrava 2010) compared with universal prescription of abacavir-based HIV therapies. One study, conducted in Singapore, considered different populations and found that testing was only cost effective for Indian populations with a higher CD4 cell count on diagnosis, due to low allele frequency in the other populations tested (Kapoor 2015).
- Kapoor R 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. PubMed PMID: 25461248.
  In Singaporean patients scheduled for treatment with either a tenofovir- or abacavir-based therapy, genotyping of HLA-B*5701 is not cost-effective for any ethnicity irrespective of the disease stage (additional costs of US$ 208,231- 926,938 per quality adjusted life-year (QALY) gained), except for Indian patients with early-stage HIV who are contraindicated to tenofovir (additional costs of US$ 44,649 per quality adjusted life-year (QALY) gained). Abacavir (as first-line) without genotyping was the cheapest and most cost-effective treatment for all ethnicities except for early-stage Indian HIV patients contraindicated to tenofovir. The HLA-B*5701 frequency, the mortality rate from abacavir-induced hypersensitivity reactions, and genotyping costs are among the major factors influencing the cost-effectiveness.
  Cost-effectiveness was estimated for the three major ethnic groups in Singapore: southern Han Chinese, Southeast Asian Malays, and South Asian Indians with HLA-B*5701 frequencies of 1.1%, 1.8%, and 6.3% respectively. Late-stage HIV was defined as patients with a CD4 count of less than 200 cells/mm^3 at initial diagnosis. The more common treatment strategies were compared, which include the following: (a) first-line abacavir-based therapy substituted with tenofovir-based therapy as second-line treatment in the event of side effects and (b) first-line tenofovir-based therapy substituted with abacavir-based therapy as second-line treatment in the event of side effects. Zidovudine-based therapy was considered as a third-line treatment, and it was assumed that patients in whom all three regimens failed would be prescribed a multiple-drug combination therapy. These alternative drugs included stavudine, lamivudine, emtricitabine, atazanavir, lopinavir, and ritonavir, which are collectively referred to as 'the hypothetical drug' in this study. All strategies including abacavir were modelled with and without HLA-B*5701 screening before prescription. For tenofovir-contraindicated patients, abacavir was considered as the first-line treatment drug; otherwise, tenofovir was also offered as the first-line treatment. For patients receiving tenofovir, the additional renal profiling and urine analysis test twice a year after the first year, because of renal dysfunction being a major side effect of tenofovir, were also included in the calculation. As were the costs of blood tests in patients on zidovudine, that may induce anaemia.
  The calculation was for life-long treatment (with a remaining life expectancy from the point of diagnosis in early-stage and late-stage HIV patients of 30 and 10 years, respectively). Only direct medical costs were included. For Chinese patients with early-stage HIV, HLA-B*5701 genotyping is found to increase quality

adjusted life-years (QALYs) by 0.0011 for an incremental cost of US$ 457 compared with the strategy with no genotyping. This corresponds to additional costs of US$ 415,845/QALY gained. The corresponding costs for late-stage Chinese patients were US$ 926,938/QALY, for Malay early-stage and late-stage HIV patients US$ 318,029/QALY and US$ 624,297/QALY, respectively, and for Indian early-stage and late-stage HIV patients US$ 208,231/QALY and US$ 284,598/QALY, respectively. Compared with a commonly cited threshold of US$ 50,000/QALY for a strategy to be cost-effective, our analyses indicated that for the patient group that can be prescribed both abacavir and tenofovir as first-line therapy, HLA-B*5701 genotyping is not cost-effective, and that first-line treatment with abacavir without genetic screening is the cheapest and the most cost-effective option irrespective of the ethnicity and disease stage. Among the subgroups of patients contraindicated to tenofovir, in whom abacavir-based therapy is considered the only first-line treatment, HLA-B*5701 genotyping is not cost-effective for Chinese and Malay patients irrespective of their disease stage (additional costs of US$ 154,490-757,270/QALY gained). However, among Indians, HLA-B*5701 genotyping before abacavir prescription is cost-effective for early-stage HIV patients, with additional costs of US$ 44,649/QALY gained, but not for late-stage HIV patients (additional costs of US$ 114,068/QALY gained). The calculation was based on average monthly cost of abacavir + lamivudine of US$ 174, average monthly cost of tenofovir + lamivudine of US$ 296, average monthly cost of zidovudine + lamivudine of US$ 132, average monthly cost of efavirenz of US$ 79, average monthly cost of hypothetical drug of US$ 408, costs of three clinician consultation for side effects of US$ 85, costs of treating abacavir hypersensitivity cases of US$ 1580, costs of treating other intolerable side effects of abacavir of US$ 32, costs involved in fatal abacavir hypersensitivity cases of US$ 31,600, costs of treating intolerable side effects of tenofovir of US$ 66, costs of treating intolerable side effects of zidovudine of US$ 32, costs of routine renal panel and urine analysis of US$ 33, and a genetic test price of US$ 277. The risks of serious adverse events were derived from the Singapore HIV database (tenofovir, abacavir, and zidovudine) and from Mallal 2008 and other published studies (abacavir hypersensitivity).

Variation of input data within the predestined ranges (for most parameters ranging from half to twice the base case value), showed the mortality rate in abacavir hypersensitivity cases to have the strongest (early- and late-stage Malay, early-stage Indian, early- and late-stage Chinese) or one but strongest (late-stage Indian) influence on the cost-effectiveness for HIV patients who can be prescribed both abacavir and tenofovir. A hypersensitivity mortality rate higher than 6.4% in Chinese patients with early-stage HIV will render HLA-B*5701 genetic screening cost-effective. The corresponding values for Malay and Indian patients with early-stage HIV are 3.2% and 4.9%, respectively. For late-stage HIV patients, the corresponding figures are 13.9%, 9.3%, and 3.3% for Chinese, Malay, and Indian HIV patients, respectively. For Indian patients with late-stage HIV, the percentage of abacavir hypersensitivity reactions in patients on abacavir without HLA-B*5701 screening had the strongest influence on the cost-effectiveness of HLA-B*5701 screening.

Among HIV patients contra-indicated to tenofovir, the mortality rate in abacavir hypersensitivity cases also had the strongest influence on the cost-effectiveness of HLA-B*5701 screening. In these patients, a higher cost of abacavir and lamivudine combination therapy (> US$ 318/month for Chinese; > US$ 248/month for Malays) or a hypersensitivity mortality rate greater than 3.7% for Chinese and 2.3% for Malays would make genetic screening cost-effective for early-stage Chinese and Malay HIV patients. In addition, for Indian early-stage HIV patients, HLA-B*5701 genetic screening is cost-effective as long as any of the following conditions are fulfilled: (i) abacavir hypersensitivity mortality rate greater than 0.62%, (ii) positive predictive value (PPV) greater than 56.5%, (iii) cost of abacavir and lamivudine combination therapy greater than US$ 170/month, (iv) progression to late-stage HIV before or at 28.4 years of treatment, or (v) Quality of Life (QoL) greater than 0.68 during early HIV. For late-stage Chinese and Malay patients, only when the abacavir hypersensitivity mortality rate is higher than 10.9% for Chinese and 6.5% for Malays will genetic screening be cost-effective. For late-stage Indian HIV patients, genetic screening will be cost-effective if any of the following conditions are fulfilled: (i) abacavir hypersensitivity mortality rate greater than 1.6%, (ii) lower cost of genetic screening (< US$ 146), or (iii) cost of abacavir and lamivudine combination therapy greater than US$ 217/month.

For early-stage patients who can be prescribed both abacavir and tenofovir, genotyping before abacavir prescription was found not to be cost-effective for the ethnicities with allele frequencies lower than 3% for any positive predictive value (PPV) of HLA-B*5701 for the development of abacavir hypersensitivity. For other ethnicities with allele frequencies greater than 3%, very high PPVs (PPV > 85%; PPV > 91.5% for Indian patients) were required for genotyping to be cost-effective). Similar results were observe for early-stage HIV patients contraindicated to tenofovir, with genotyping not being cost-effective for ethnicities with allele frequencies lower than 3% for any PPV. However, for allele frequencies greater than 3%, screening was cost-effective for relatively smaller PPVs. At the current PPV of 61.2%, genotyping will be cost-effective for ethnicities with HLA-B*5701 allele frequencies greater than 5.6% (for patients contraindicated to tenofovir; cost-effective if PPV > 56.5% for Indian patients), which agrees with our results for Indian patients in this group.

Late-stage HIV patients exhibited similar trends to early-stage HIV patients, where patients receptive to both abacavir and tenofovir required both significantly higher PPV and allele frequency, whereas in tenofovir-contraindicated patients there was a rapid decrease in the cost-effective threshold PPV with an increase in allele frequency. HLA-B*5701 genotyping was found not to be cost-effective for ethnicities with allele frequencies lower than 6% for any PPV in both these patient categories.

Varying all input data simultaneously confirmed that for a cost-effectiveness threshold of US$ 50,000/QALY, HLA-B*5701 screening was not cost-effective for all Chinese and Malay HIV patients irrespective of disease stage, as well as all Indian HIV patients except early-stage patients who are contraindicated to tenofovir (with 0-20% of simulations reporting cost-effectiveness in these patient groups). For these patients, 75-91% of simulations reported abacavir without genotyping to be cost-effective. Conversely, HLA-B*5701 screening was found to be cost-effective in 51% of the simulations for early-stage Indian HIV patients contraindicated to tenofovir.

- Cargnin S et al. Diagnostic accuracy of HLA-B*57:01 screening for the prediction of abacavir hypersensitivity and clinical utility of the test: a meta-analytic review. Pharmacogenomics 2014;15:963-76. PubMed PMID: 24956250.
  Reanalysis of the costs per abacavir hypersensitivity reaction avoided, confirmed that HLA-B*5701 testing is cost-effective, with these costs being lower than previously estimated.
  The calculation in Kauf 2010 and Nieves Calatrava 2010 (Nieves Calatrava D et al. Cost-effectiveness analysis of HLA-B*5701 typing in the prevention of hypersensitivity to abacavir in HIV+ patients in Spain. Enferm Infecc Microbiol Clin 2010;28:590-5. PubMed PMID: 20144493) was repeated with the RR of 0.106 determined in a meta-analysis of 5 studies comparing HLA-B*5701-guided with not HLA-B*5701-guided therapy.
- Kauf TL et al. Economic efficiency of genetic screening to inform the use of abacavir sulfate in the treatment of HIV. Pharmacoeconomics 2010;28:1025-39. PubMed PMID: 20575592.
  Over the first 60 days of treatment of patients in the USA, prospective HLA-B*5701 screening prior to abacavir initiation costs an additional $US 17 per patient and avoided 537 hypersensitivity reactions per 10,000 patients, resulting in additional costs of US$ 328.32 per hypersensitivity reaction avoided. Because of the very modest costs for avoidance of hypersensitivity reactions, the authors conclude that HLA-B*5701 screening prior to abacavir initiation is likely to be considered a cost-effective use of scarce medical resources. The per-patient cost of screening was sensitive to the cost of the genetic test, hypersensitivity reaction costs and screening performance (i.e. the negative predictive value). At a test cost of US$ 71 or less or at clinically diagnosed hypersensitivity costs of more than US$ 1326, prospective screening is cost saving compared with not screening. In the lifetime model, screening-informed abacavir use was more effective and less costly than initiation with a tenofovir-containing regimen (about US$ 285,000 less costs per quality adjusted life-year gained and about US$ 5000 less costs per patient). Screening remained more effective and less costly if input data were varied.
  The calculation was from a comprehensive health-care payer perspective. Costs were calculated for the first 60 days or for life-long treatment (with a remaining life expectancy from the point of diagnosis of 40 years). Genotype-guided therapy (abacavir and lamivudine plus efavirenz for HLA-B*5701-negative patients and tenofovir and emtricitabine plus efavirenz for HLA-B*5701-positive patients) was compared to non-genotype guided therapy (abacavir and lamivudine plus efavirenz for all for the 60 days period and tenofovir and emtricitabine plus efavirenz for all for the life-time period). Abacavir-induced hypersensitivity reactions and tenofovir-related renal failure (yearly probability of 0.87%) were considered as short-term drug-associated adverse events. In the life-time model, also efficacy parameters were included. Only direct medical costs were included. The calculation was based on costs of a patient-suspected hypersensitivity reaction of US $ 116.14, costs of a clinically diagnosed hypersensitivity reaction of US$ 998.11, costs of renal failure monitoring of US$ 0.00, costs of tenofovir-related renal toxicity of US$ 100.00, costs of abacavir 600 mg and lamivudine 300 mg of US$ 906.85 per 30 days, costs of tenofovir 200 mg and emtricitabine 300 mg of US$ 1008.32 per 30 days, costs of lamivudine 150 mg and zidovudine 300 mg of US$ 838.94 per 30 days, costs of efavirenz 600 mg of US$ 578.83 per 30 days, costs of lopinavir 200 mg and ritonavir 50 mg of US$ 841.90 per 30 days, and a genetic test price of US$ 87.92. To also take into account the effects of patients and clinicians knowing whether there was a high or low risk of a hypersensitivity reaction, data were derived from a large clinical trial, in which abacavir-naïve patients were prospectively screened for HLA-B*5701 (Young B et al. First large, multicenter, open-label study utilizing HLA-B*5701 screening for abacavir hypersensitivity in North America. AIDS 2008; 22:1673-5). The HLA-B*5701 prevalence was 5.66% and the negative predictive value 99.23%, resulting in an estimated abacavir hypersensitivity reaction incidence without screening of 6%. Data from resource use by patients using abacavir or tenofovir were derived from 5 physicians. The false hypersensitivity reaction rate was 3% with HLA-B*5701 screening and 50% without screening.
- Wolf E et al. Cost impact of prospective HLA-B*5701-screening prior to abacavir/lamivudine fixed dose combination use in Germany. Eur J Med Res 2010;15:145-51. PubMed PMID: 20554495.
  In German patients using abacavir-based therapy, potential cost savings of implementing HLA-B*5701 screening were estimated at € 44 and € 127 per screened patient, from a healthcare payer or societal perspective respectively.
  The calculation was from a health-care payer or societal perspective (direct medical costs and direct plus indirect costs included, respectively, with indirect costs including costs for productivity loss due to temporary disability to work). Costs were calculated for a 6-week period or until remission of the abacavir-related hypersensitivity reaction. The calculation was based on costs for outpatient care of € 73, hospital costs for cases receiving inpatient care of € 6,904, extra charge for patients with private health insurance of € 1,884 (for a single room or chief physician attendance), indirect costs of € 873, costs of abacavir plus lamivudine

of € 758 per month (of which 53.7% was discarded upon a hypersensitivity reaction), costs of concomitant medication of € 20, and a genetic test price of € 86. Costs for replacing abacavir plus lamivudine by another drug combination were not included. Resource consumption related to an abacavir hypersensitivity reaction was estimated based on data of patients using abacavir without prior HLA-B*5701 screening from three HIV outpatient care units (private practices) and two university hospital units specialised in HIV/AIDS. Other data on abacavir hypersensitivity reactions were derived from Mallal 2008, Zucman 2007, Rauch 2006 and 32 not genotyped cases of clinically suspected abacavir hypersensitivity reactions. Based on these data, a 10% rate of clinically suspected hypersensitivity reactions in Germany (HLA-B*5701 prevalence of 7.3%) was estimated. A negative predictive value of the HLA-B*5701 screening of 99.5% was assumed.
Variation of input data found the prevalence of HLA-B*5701 to have the largest influence on the costs saved by HLA-B*5701 screening, followed by costs for inpatient care, costs of HLA-B*5701 screening, and hypersensitivity reaction hospitalisation rate. Total cost savings ranged from € 16 to € 254. For direct costs, results ranged from additional costs of € 43 to cost savings of € 152.

- Schackman BR et al. The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. AIDS 2008;22:2025-33. PubMed PMID: 18784465.
For patients in the USA, HLA-B*5701 testing prior to treatment with abacavir, lamivudine, and efavirenz resulted in additional costs of US$ 36,700 per quality adjusted life year (QALY) gained compared to no testing. At the commonly accepted threshold of US$ 50,000-100,000 per QALY gained, this is cost-effective. HLA-B*5701-guided therapy consisted of abacavir, lamivudine, and efavirenz for HLA-B*5701-negative patients and tenofovir, emtricitabine, and efavirenz for HLA-B*5701-positive patients. Initiating treatment with tenofovir, emtricitabine, and efavirenz increased costs without improving QALYs compared to abacavir-based treatment. HLA-B*5701 testing remained the preferred strategy only if abacavir-based treatment had equal efficacy and costed less per month than tenofovir-based treatment. Results were also sensitive to the cost of HLA-B*5701 testing and the prevalence of HLA-B*5701. At genetic test costs of US$ 68, the additional costs per QALY gained remained below $50,000 as long as the prevalence of HLA-B*5701 was greater than 3.6%. At genetic test costs of US$ 136, this threshold was 7.4%.
The calculation was for a life-time period. Only direct medical costs were included. Patients taking abacavir who developed a suspected hypersensitivity reaction were then switched to tenofovir-based treatment. Patients switched to tenofovir-based treatment who subsequently developed treatment-limiting tenofovir-associated nephrotoxicity were switched to zidovudine, lamivudine, and efavirenz. For patients initiating tenofovir-based treatment who developed treatment-limiting tenofovir-associated nephrotoxicity, three alternatives to guide drug substitution were considered: 1) HLA-B*5701 testing with those testing HLA-B*5701 negative switched to abacavir-based treatment and those testing HLA-B*5701 positive switched to zidovudine-based treatment, 2) substituting abacavir-based treatment without testing, and 3) substituting zidovudine-based treatment without testing. Abacavir-based treatment without HLA-B*5701 testing resulted in a projected 30.93 years life expectancy, 16.23 QALYs, and US$ 472,200 lifetime cost per person. HLA-B*5701 testing added 0.04 quality-adjusted months at an incremental cost of $110, resulting in additional costs of US$ 36,700 per QALY gained compared to no testing. Initiating treatment with a tenofovir-based regimen increased costs (additional costs of US$ 230 compared to abacavir with HLA-B*5701 testing) without improving QALYs. Substituting the more toxic, less effective zidovudine-based regimen if treatment-limiting nephrotoxicity occurs resulted in 0.07 fewer quality-adjusted life months compared to abacavir with HLA-B*5701 testing. The calculation was based on monthly costs of abacavir, lamivudine and efavirenz of US$ 1,135, monthly costs of tenofovir, emtricitabine and efavirenz of US$ 1,139, monthly costs of zidovudine, lamivudine and efavirenz of US$ 1,081, monthly costs of subsequent regimens ranging from US$ 1,549 to US$ 3,338, costs of a mild hypersensitivity reaction treated in an outpatient setting of US$ 105, costs of a severe non-fatal hypersensitivity reaction of US$ 3,566, costs of a severe fatal hypersensitivity reaction of US$ 31,999, costs of treatment-limiting nephrotoxicity of US$ 194, and a genetic test price of US$ 68. Immunological confirmation of hypersensitivity reactions was assumed not to occur. Probabilities of adverse reactions were derived from published studies (including Mallal 2008). Despite an average HLA-B*5701 carrier prevalence of 4.4% in US HIV patients, the calculation was based on the HLA-B*5701 carrier prevalence of 5.7% from Mallal 2008.
Variation of input data showed the additional costs of HLA-B*5701 testing to be US$ 45,200 per QALY gained if 4.4% of patients is HLA-B*5701 carrier, as is the case in US HIV patients. This is still cost-effective, both at a threshold of US$ 50,000 per QALY gained and at a threshold of US$ 100,000 per QALY gained. With genetic test costs of US$ 68, the additional costs per QALY gained remained below $100,000 as long as the prevalence of HLA-B*5701 was greater than 1.4% and remained below $50,000 as long as the prevalence of HLA-B*5701 was greater than 3.6%. At twice the test costs (US$ 136 per test), these thresholds became 2.9% and 7.4%.
- Hughes DA et al. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. Pharmacogenetics 2004;14:335-42. PMID 15247625.
In UK HIV patients, routine testing for HLA-B*5701 ranged from being cost-saving and better (nevirapine, efavirenz, or didanosine as alternatives for abacavir) to additional costs of € 22,811 (indinavir plus ritonavir as alternative) per hypersensitivity reaction avoided, depending on the choice of alternative therapy. This indicates that HLA-B*5701 testing before starting abacavir is cost-effective.

The calculation was from the perspective of the UK National Health Service. Costs were calculated for a 6-month period. Only direct medical costs were included. Patients initiating antiretroviral therapy were assumed to receive abacavir, lamivudine and zidovudine. In the case of salvage therapy, patients were assumed to receive regimens containing abacavir. Abacavir was substituted with another drug (didanosine or tenofovir in the case of salvage therapy) for patients testing positive for HLA-B*5701 or developing a hypersensitivity reaction. The calculation was based on costs of inpatient hospitalisation of € 614 per night, costs of an outpatient clinic visit of € 21, costs of attendance via the ward of € 131, hypersensitivity costs of € 2611, costs of abacavir 300 mg twice a day of € 341 per month, costs of abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg twice a day of € 830 per month, costs of nevirapine 200 mg (start once daily, twice a day thereafter) and zidovudine 300 mg and lamivudine 150 mg twice a day of € 810 per month, costs of efavirenz 600 mg once daily and zidovudine 300 mg and lamivudine 150 mg twice a day of € 730 per month, costs of nelfinavir 750 mg three times a day and zidovudine 300 mg and lamivudine 150 mg twice a day of € 964 per month, costs of lopinavir 400 mg, ritonavir 100 mg, zidovudine 300 mg and lamivudine 150 mg twice a day of € 903 per month, costs of saquinavir 1000 mg, ritonavir 100 mg, zidovudine 300 mg and lamivudine 150 mg twice a day of € 1177 per month, costs of indinavir 800 mg, ritonavir 100 mg, zidovudine 300 mg and lamivudine 150 mg twice a day of € 1323 per month, costs of didanosine 200 mg twice a day of € 251 per month, costs of tenofovir 245 mg twice a day of € 364 per month, and a genetic test price of € 43.40. The risks of serious adverse events were derived from published data (including Symonds W et al. Risk factor analysis of hypersensitivity reactions to abacavir. Clin Ther 2002;24:565-73) and from data from a UK HIV clinic. In the UK HIV clinic, six (46%) of the abacavir hypersensitive patients were HLA-B*5701-positive, compared to five (10%) of the non-hypersensitive patients (OR = 7.9; 95% CI 1.5–41.4 (S)). Pooling of these data with published data (Mallal 2002 and Hetherington 2002) resulted in a pooled OR of 29 (95% CI: 6.4–132.3 (S)). Information on the patterns of care and health care resource utilisation of hypersensitivity patients was derived from the UK HIV clinic data.
Variation of input data showed the cost of the alternative therapies to be most influential on the additional costs per hypersensitivity reaction avoided, followed by the probability of developing a hypersensitivity reaction.

Date of literature search: 21 October 2022.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	HLA-B*5701	4F	Yes	Yes	7 February 2023

Mechanism:
Experimental data suggest the following mechanism of hypersensitivity reactions to abacavir:
Abacavir binds non-covalently in the peptide binding groove of HLA-B*5701 and in this way changes the repertoire of peptides bound by HLA-B*5701. As a result, self-peptides that do not bind to HLA-B*5701 in the absence of abacavir, do bind in the presence of abacavir. Because these HLA-peptide complexes are new, immune cells consider the bound peptides as foreign and trigger an immune response against cells containing abacavir.
In addition, there are some indications that immune cells might also consider the HLA-B*5701 itself as new and thus foreign after abacavir binding, so without self-peptides being bound.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	

• CTCAE Grade 5 (clinical effect score F)	++	++
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	++
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	++
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	9+
Corresponding Clinical Implication Score:		Essential