Abacavir Hypersensitivity Reaction Reporting Rates in a Decade of HLA-B*5701 Screening as a Risk Mitigation Measure

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Introduction

- Abacavir (ABC) hypersensitivity reaction (HSR) is a well-characterised systemic syndrome[1]
- HLA-B*5701 screening identifies patients at increased risk for HSR[2]
- Screening was adopted in Company clinical trials from 2007 and in clinical practice from 2008
- Meta-analyses of Company trials that were conducted pre–HLA-B*5701 screening reported HSR rates of 4% to 8%[3]
- This analysis assesses the effectiveness of HLA-B*5701 screening on reducing HSR rates in clinical trial and real-world settings

Methods

- A meta-analysis was performed on results from 12 Company clinical trials with 3063 HLA-B*5701–negative patients who received either ABC/dolutegravir (DTG)/lamivudine (3TC) or ABC/3TC with a separate anchor drug
- Potential cases were identified using pre-specified terms (Drug hypersensitivity, Hypersensitivity, Anaphylactic reaction, Anaphylaxis) and then adjudicated against a Company ABC HSR case definition (Box 1) used for regulatory reporting
- Investigator-diagnosed cases were also identified, and rates were calculated
- The same case definition was also used to identify spontaneously reported cases for four marketed ABC products, and reporting rates (cases per patient-years [PY] of exposure) were calculated using estimated exposure from sales data.* Data for December 1998 were included in 1999

Box 1. Company ABC HSR Case Definition

A case of ABC HSR is one in which conditions in **A** OR **B** are fulfilled and the exclusion criteria do not apply:

A: Hypersensitivity, anaphylactic reaction, allergic reaction, or drug allergy **to ABC** is reported; OR

B: Two or more events are reported from two or more of the following groups of signs/symptoms: (1) Rash; (2) Fever; (3) Gastrointestinal symptoms *(nausea, vomiting, diarrhoea, abdominal pain)*; (4) Constitutional symptoms *(lethargy, fatigue, malaise, myalgia, arthralgia, general ill feeling)*; or (5) Respiratory symptoms *(dyspnoea, sore throat, cough, chest x-ray changes, predominantly infiltrates, which can be localised)*

Exclusion criteria
- Other causes of the HSR-like events appear significantly more likely
- Cases in which there is a negative re-challenge with ABC
- Cases in which symptoms resolved with continued ABC treatment
- Cases of possible ABC HSR [in Part A†] that do not fulfill the criteria in Part B

†**Note:** Applied to clinical trial meta-analysis only, because cases were captured in more detail in clinical trials than in most spontaneous reports of clinically suspected ABC HSR.

Results

Clinical Trial Meta-analysis

- Data from 3063 patients were analysed. The ABC/DTG/3TC Sub-population had more females (Table 1), ART experience, lower viral loads (VL), and higher CD4 counts at baseline (BL; Table 2) than the ABC/3TC + non-DTG anchor Sub-population
  - These differences were not considered to influence reporting rates
- Rates for suspected ABC HSR were ≤1% (0.3%-1.3%) in each of the different sub-analyses performed (Table 3), with lower rates for ABC/DTG/3TC (0.3%-0.4%) than ABC/3TC + non-DTG anchor (0.8%-1.3%)
- Rates for Investigator-diagnosed ABC HSR and Company-adjudicated cases were similar in each ABC-exposed population analysed (Table 3)
- None of the suspected ABC HSR cases resulted in a fatal outcome

Table 1. Clinical Trial Patient Baseline Demographics

Characteristic	All ABC Exposed Patients[a] (N=3063)	ABC/DTG/3TC Sub-Population[b] (N=1494)	ABC/3TC Sub-Population[c] (N=1569)
Age, median (range), y	38.0 (18.0, 80.0)	39.0 (18.0, 80.0)	37.0 (18.0, 75.0)
Gender, n (%)			
Female	699 (22.8)	454 (30.4)	245 (15.6)
Male	2364 (77.2)	1040 (69.6)	1324 (84.4)
Race, n (%)			
White	2105 (68.7)	987 (66.1)	1118 (71.3)
Non-White	956 (31.2)	505 (33.8)	451 (28.7)
Missing	2 (0.1)	2 (0.1)	0
Geographic region, n (%)			
Europe[d]	911 (29.7)	416 (27.8)	495 (31.5)
North America[e]	1881 (61.4)	881 (59.0)	1000 (63.7)
South America[f]	38 (1.2)	34 (2.3)	4 (0.3)
Rest of world[g]	233 (7.6)	163 (10.9)	70 (4.5)

[a]Patients exposed to ABC/3TC or ABC/DTG/3TC. [b]Patients exposed to ABC/DTG/3TC or DTG+ABC/3TC. [c]Patients exposed to ABC/3TC in combination with a non-DTG anchor drug, which was atazanavir + ritonavir (RTV), cabotegravir, darunavir+RTV, efavirenz, or raltegravir. [d]Included: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Latvia, Netherlands, Portugal, Romania, Spain, Switzerland, United Kingdom. [e]Included: Canada, United States of America. [f]Included: Argentina, Mexico, Puerto Rico. [g]Included: Australia, Russia, South Africa, Thailand.

Table 2. Clinical Trial Patient Baseline Clinical Characteristics

Characteristic	All ABC Exposed Patients[a] (N=3063)	ABC/DTG/3TC Sub-Population[b] (N=1494)	ABC/3TC Sub-Population[c] (N=1569)
ART status, n (%)			
Naive	2345 (76.6)	975 (65.3)	1370 (87.3)
Experienced	718 (23.4)	519 (34.7)	199 (12.7)
VL & CD4, median (range)			
HIV-1 RNA (log_{10} c/mL)	4.36 (1.59, 6.93)	4.02 (1.59, 6.66)	4.64 (1.59, 6.93)
CD4+ count (cells/mm^3)	363 (10, 1831)	411 (19, 1831)	313 (10, 1196)
CDC classification, n (%)			
A	2408 (78.6)	1183 (79.2)	1225 (78.1)
B	415 (13.6)	190 (12.7)	225 (14.3)
C	240 (7.8)	121 (8.1)	119 (7.6)

[a]Patients exposed to ABC/3TC or ABC/DTG/3TC. [b]Patients exposed to ABC/DTG/3TC or DTG+ABC/3TC. [c]Patients exposed to ABC/3TC in combination with a non-DTG anchor drug, which was atazanavir + ritonavir (RTV), cabotegravir, darunavir+RTV, efavirenz, or raltegravir.

Table 3. Clinical Trial Reporting Rates of Suspected ABC HSR Among HLA-B*5701–Negative Patients From 2007 to 2016

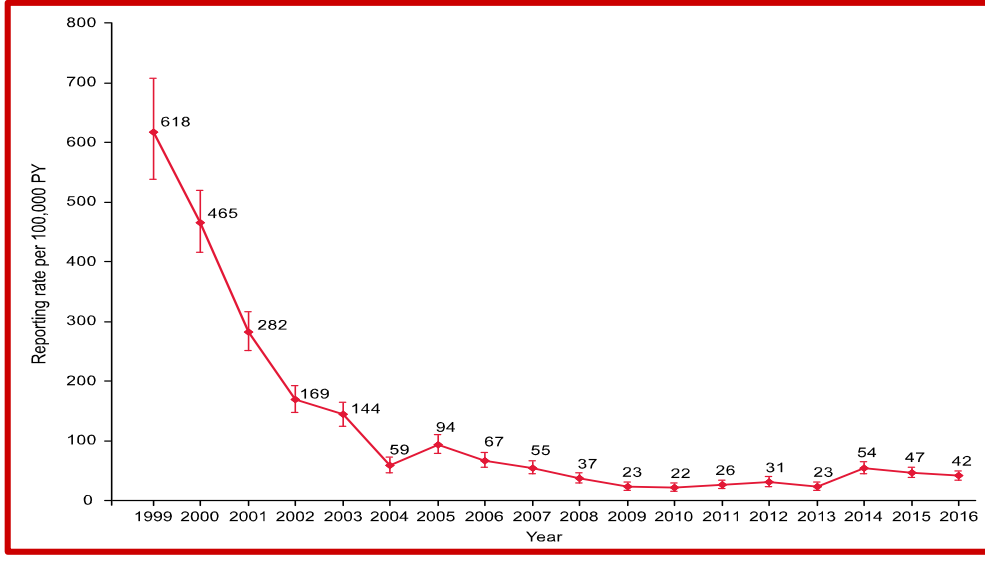
Case Analysis, Rates (95% CI)[a]	All ABC Exposed Patients[b] (N=3063)	ABC/DTG/3TC Sub-Population[c] (N=1494)	ABC/3TC Sub-Population[d] (N=1569)
Investigator-diagnosed ABC HSR	0.6% (0.32-0.89) [n=17]	0.3% (0.07-0.68) [n=4]	0.8% (0.44-1.41) [n=13]
Company-adjudicated cases	0.7% (0.42-1.05) [n=21]	0.3% (0.11-0.78) [n=5]	1.0% (0.58-1.65) [n=16]
All possible cases of ABC HSR[e]	0.9% (0.58-1.28) [n=27]	0.4% (0.15-0.87) [n=6]	1.3% (0.83-2.04) [n=21]

[a]95% confidence intervals (CIs) were calculated based on exact binomial 2-sided CIs. [b]Patients exposed to ABC/3TC or ABC/DTG/3TC. [c]Patients exposed to ABC/DTG/3TC or DTG+ABC/3TC. [d]Patients exposed to ABC/3TC in combination with a non-DTG anchor drug, which was atazanavir + ritonavir (RTV), cabotegravir, darunavir+RTV, efavirenz, or raltegravir. [e]Investigator-diagnosed ABC HSR and Company-adjudicated cases combined.

Spontaneous Reporting

- Rates (Figure 1) decreased on an annual basis since ABC was first marketed through to 2007 (618 to 55 cases per 100,000 PY), with further decreases from 2008 (37 to 22 cases per 100,000 PY)
- A numerical increase was observed for 2014 (54 cases per 100,000 PY); however, rates subsequently decreased toward previous levels
- The cumulative rate for fatality associated with suspected ABC HSR was 1 case per 100,000 PY, from 1998 to 2016

Figure 1. Annual Spontaneous Reporting Rates for Cases Fulfilling the Company ABC HSR Case Definition to 31 Dec 2016[a]



95% CIs were calculated based on Wald's Method. [a]Pooled analysis of all ABC-containing products (ABC/3TC/zidovudine, ABC/3TC, ABC/DTG/3TC).

Conclusions

- Clinically suspected ABC HSR rates were ≤1% in the HLA-B*5701–negative clinical trial patients included in this analysis
- Recognising the limitations of spontaneously reported data, following adoption in 2008, HLA-B*5701 screening appears to have reduced reporting rates of suspected HSR in clinical practice
- Clinically suspected ABC HSRs rarely resulted in fatal outcome
- Where HLA-B*5701 screening is standard of care, patients should be confirmed negative for this allele before starting ABC treatment

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