Background: We aimed to assess the value of a structured clinical assessment and genetic testing for refining the diagnosis of abacavir hypersensitivity reactions (ABC-HSRs) in a routine clinical setting.

Methods: We performed a diagnostic reassessment using a structured patient chart review in individuals who had stopped ABC because of suspected HSR. Two HIV physicians blinded to the human leukocyte antigen (HLA) typing results independently classified these individuals on a scale between 3 (ABC-HSR highly likely) and -3 (ABC-HSR highly unlikely). Scoring was based on symptoms, onset of symptoms and comedication use. Patients were classified as clinically likely (mean score ≥ 2), uncertain (mean score ≥ -1 and ≤ 1) and unlikely (mean score ≤ -2). HLA typing was performed using sequence-based methods.

Results: From 131 reassessed individuals, 27 (21%) were classified as likely, 43 (33%) as unlikely and 61 (47%) as uncertain ABC-HSR. Of the 131 individuals with suspected ABC-HSR, 31% were HLA-B*5701-positive compared with 1% of 140 ABC-tolerant controls (P < 0.001). HLA-B*5701 carriage rate was higher in individuals with likely ABC-HSR compared with those with uncertain or unlikely ABC-HSR (78%, 30% and 5%, respectively, P < 0.001). Only six (7%) HLA-B*5701-negative individuals were classified as likely HSR after reassessment.

Conclusions: HLA-B*5701 carriage is highly predictive of clinically diagnosed ABC-HSR. The high proportion of HLA-B*5701-negative individuals with minor symptoms among individuals with suspected HSR indicates overdiagnosis of ABC-HSR in the era preceding genetic screening. A structured clinical assessment and genetic testing could reduce the rate of inappropriate ABC discontinuation and identify individuals at high risk for ABC-HSR.

Introduction

The major treatment-limiting adverse effect of abacavir (ABC) treatment for HIV infection is a multisystem drug hypersensitivity reaction (HSR) that occurs in approximately 5% of Caucasians [1–3]. The diagnosis of this syndrome is based on the onset of ≥2 clinical symptoms from a list that includes rash, fever, gastrointestinal and respiratory symptoms, myalgia, lethargy and malaise [1–6]. The use of broad diagnostic criteria has ensured that potential abacavir hypersensitivity reactions (ABC-HSRs) are recognized, given that a missed diagnosis could result in a potentially fatal HSR. However, these symptoms are relatively non-specific and can also be caused by an intercurrent illness or side effects of concurrently prescribed drugs. Accordingly, double-blinded clinical trials have consistently revealed an approximately 3% rate of ‘false-positive’ diagnoses of ABC-HSR among patients who were not exposed to the drug [7].

It has been established that genetic susceptibility to ABC-HSR is strongly associated with HLA-B*5701 carriage [3,4,6,8–11]. These findings have now been confirmed by the PREDICT-1 and SHAPE trials [5], in
which immunologically confirmed cases of HLA-B*5701 ABC-HSR (utilizing ABC patch testing) were universally associated with HLA-B*5701 carriage. Accordingly, HIV treatment guidelines in the United States (Department of Health and Human Services) and Europe (European AIDS Clinical Society) now recommend HLA-B*5701 screening before prescribing ABC therapy.

Although these guidelines appear to pave the way for a pharmacogenetic approach to ABC prescription in ABC-naive patients, there is a large number of patients with an archived diagnosis of ABC-HSR based solely on clinical assessment, for whom permanent avoidance of ABC treatment has been advised. In order to better understand the characteristics of these patients, we have undertaken a retrospective analysis of suspected ABC-HSR individuals recorded within the Swiss HIV Cohort Study (SHCS) in the era prior to genetic screening.

We aimed to investigate whether a structured clinical reassessment of suspected ABC-HSR patients would refine the diagnoses of ABC-HSR in a routine clinical setting and to assess the correlation between clinical ABC-HSR diagnoses and genetic susceptibility. We further aimed to investigate whether combining a refined clinical assessment with genetic testing would allow a reliable distinction of individuals at high risk for severe ABC-HSR from individuals with unspecific symptoms caused by concurrent illnesses or by other drugs who could safely continue ABC.

Methods

Study population

The study participants were recruited from the SHCS, a prospective cohort study with ongoing enrolment of adult HIV-infected patients. As of December 2007, a total of 14,848 individuals have been enrolled. Patients were followed-up in one of seven study centres. Clinical and laboratory information was collected according to standardized criteria on structured forms at enrolment and at follow-up visits at 6-month intervals. Written informed consent was mandatory for inclusion in the study and the study was approved by all local ethical committees.

The reason for stopping an antiretroviral drug is recorded for all SHCS participants in a central database. Stopping a drug because of suspected HSR has been recorded routinely since 2000. This definition of HSR, which is based purely on clinical judgment by the physician in charge and does not rely on standardized criteria or on knowledge about the genetic susceptibility, was termed ‘suspected ABC-HSR’. We included all SHCS participants stopping ABC because of suspected ABC-HSR as recorded in the SHCS database until March 2005. ABC tolerance was defined as receiving ABC for ≥6 weeks without signs of ABC-HSR. ‘ABC-tolerant’ individuals (n=140) who had been human leukocyte antigen (HLA)-typed within the framework of the SHCS in research projects unrelated to drug HSR studies served as ABC-tolerant controls.

Structured clinical reassessment

For each recorded case of suspected ABC-HSR, information from primary clinical records was collected by physicians blinded to the HLA typing results and collated in a standard form that incorporated four characteristics: time of starting ABC, time to onset of symptoms and time of resolution of symptoms after ABC cessation; concomitant drug therapy; characteristics of cutaneous symptoms; and presence or absence of fever, rash, gastrointestinal (nausea and vomiting), respiratory or constitutional symptoms. Two experienced HIV physicians (CT and CAF), assessed the likelihood of an ABC-HSR based on the synthesis of these data regarding the time course of ABC-HSR, concomitant drug therapy and clinical symptoms. The two physicians, blinded to the HLA typing results, independently classified suspected ABC-HSR on a scale between 3 (ABC-HSR highly likely) and -3 (ABC-HSR highly unlikely). Patients were then classified on the basis of the mean of the two reassessment scores as clinically unlikely ABC-HSR (mean score ≤-2), clinically uncertain ABC-HSR (mean score ≥-1 and ≤1) and clinically likely ABC-HSR (mean score ≥2).

The symptoms related to ABC-HSR were classified according to the ABC medication guide, which has been approved by the US Food and Drug Administration. General ill-feeling, tiredness and myalgia were grouped as constitutional symptoms; dyspnea, cough and a sore throat were grouped as respiratory symptoms; and abdominal pain, diarrhoea, nausea and vomiting were grouped as gastrointestinal symptoms. However, because the symptoms were assessed retrospectively by an independent review of medical records, the absence of a symptom did not guarantee that the symptom did not occur at the time of ABC-HSR diagnoses. As not all clinical information pertinent to HSR was available from the medical records and because there is no validated scoring system for diagnosing clinical ABC-HSR, this classification process relied on standard diagnostic criteria available to HIV physicians and did not impose any additive scoring system based on the presence or absence of symptoms or severity of symptoms. The two physicians were also blinded to the time to resolution of symptoms and to the further course of the treatment in order to accurately represent the available clinical information at the time of ABC-HSR.

HLA typing

DNA was extracted from whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Victoria, Australia)
following the manufacturer’s guidelines. Exons 2 and 3 were sequenced using Big dye terminator sequencing reactions (ABI PE, Foster City, CA, USA) using primers specific for exons 2 and 3. Allele assignments were obtained using the Assign programme (Conexio Genomics, Applecross, Australia). Ambiguities were resolved by sequencing with allele-specific subtyping primers. High-resolution HLA typing was performed at the HLA-B and HLA-DRB1 locus as these loci have been most consistently associated with HSR.

ABC patch testing

Epicutaneous patch testing was performed as previously described [6,12] in a subgroup of 23 individuals with suspected ABC-HSR, recruited from two of the seven SHCS centres with access to this diagnostic method. All individuals followed in one of these two centres who stopped ABC because of suspected ABC-HSR and who gave informed consent for patch testing were included. Patch test reactions were read after 48 h. A positive result required the absence of an allergic reaction to the control vehicle and demonstration of erythema and vesicular rash limited to the patch area. The median time from initiating ABC to the patch tests was 34.2 months (interquartile range 27.3–39.0).

Table 1. Clinical and demographic characteristics of individuals with suspected ABC-HSR and of ABC-tolerant controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Suspected ABC-HSR, n=149</th>
<th>ABC-tolerant, n=1,728</th>
<th>Odds ratio (95% CI)*</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>106 (71)</td>
<td>1,216 (70)</td>
<td>0.96 (0.66–1.39)</td>
<td>0.8</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>White, n (%)</td>
<td>138 (93)</td>
<td>1,451 (84)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>7 (5)</td>
<td>170 (10)</td>
<td>0.43 (0.2–0.94)</td>
<td>0.03†</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>4 (3)</td>
<td>107 (6)</td>
<td>0.39 (0.14–1.08)</td>
<td>0.07</td>
</tr>
<tr>
<td>HIV transmission risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual, n (%)</td>
<td>59 (40)</td>
<td>662 (38)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Heterosexual, n (%)</td>
<td>34 (23)</td>
<td>621 (36)</td>
<td>0.61 (0.40–0.95)</td>
<td>0.03†</td>
</tr>
<tr>
<td>Intravenous drug use, n (%)</td>
<td>51 (34)</td>
<td>383 (22)</td>
<td>1.49 (1.01–2.21)</td>
<td>0.05†</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>5 (3)</td>
<td>62 (4)</td>
<td>0.90 (0.35–2.33)</td>
<td>0.83</td>
</tr>
<tr>
<td>Immunological status*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ T-cell count &gt;500 cells/µl, n (%)</td>
<td>39 (28)</td>
<td>503 (31)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>CD4+ T-cell count 200–500 cells/µl, n (%)</td>
<td>52 (37)</td>
<td>739 (45)</td>
<td>0.90 (0.59–1.39)</td>
<td>0.7</td>
</tr>
<tr>
<td>CD4+ T-cell count &lt;200 cells/µl, n (%)</td>
<td>49 (35)</td>
<td>405 (24)</td>
<td>1.56 (1.0–2.4)</td>
<td>0.05†</td>
</tr>
<tr>
<td>Prior CDC class C, n (%)</td>
<td>54 (36)</td>
<td>484 (28)</td>
<td>1.50 (1.02–2.07)</td>
<td>0.03†</td>
</tr>
<tr>
<td>Treatment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART-naive, n (%)§</td>
<td>16 (11)</td>
<td>185 (11)</td>
<td>1.00 (0.58–1.72)</td>
<td>0.9</td>
</tr>
<tr>
<td>Use of NNRTI, n (%)§</td>
<td>46 (31)</td>
<td>536 (31)</td>
<td>0.99 (0.69–1.42)</td>
<td>0.9</td>
</tr>
<tr>
<td>Use of PI, n (%)§</td>
<td>61 (41)</td>
<td>643 (37)</td>
<td>1.16 (0.83–1.64)</td>
<td>0.4</td>
</tr>
<tr>
<td>Detectable HIV RNA (&gt;400 copies/ml), n (%)§</td>
<td>80 (58)</td>
<td>737 (45)</td>
<td>1.66 (1.17–2.36)</td>
<td>0.004†</td>
</tr>
</tbody>
</table>

*Univariate logistic regression. †Statistical significance P<0.05. §The closest available CD4+ T-cell count and HIV RNA measurement before starting abacavir (ABC) was used for analysis. ‡Before starting ABC. *Concomitant use with ABC. The median time from the laboratory measurement to the start of ABC was 12 days (interquartile range [IQR] 0–31) for CD4+ T-cell counts and 10 days (IQR 0–29) for HIV RNA measurements. A total of 90 (5%) individuals did not have immunological and virological data within 6 months prior or 2 weeks after starting ABC and did not contribute to this analysis. Age (median 41 years) and CD8+ T-cell counts (median 860 cells/µl) did not differ significantly between the two groups. ART, antiretroviral therapy; HSR, hypersensitivity reaction; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Ref, reference.
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Drug use (IDU) was associated with a higher risk of ABC-HSR, and HIV transmission through heterosexual contact with a lower risk of ABC-HSR as compared with the reference group (HIV transmission through homosexual contact).

In multivariate logistic regression (considering the significant univariate effects of ethnicity, HIV transmission mode, CD4+ T-cell counts, HIV RNA and prior AIDS events), only a detectable HIV RNA when starting ABC remained significantly associated with the diagnosis of an ABC-HSR (OR 1.64, 95% confidence interval [CI] 1.08–2.48, P=0.02).

Structured clinical reassessment of 131 individuals with suspected ABC-HSR

From the 149 patients with suspected ABC-HSR, 8 individuals were excluded as we could not retrieve any additional information on symptoms or onset of symptoms. Seven were excluded because of the lack of stored samples for HLA typing and six because HLA sequencing failed as a result of poor sample DNA quality. Three individuals with a suspected ABC-HSR prior to January 2000 were additionally included because the diagnosis had been noted in the database retrospectively. A total of 131 individuals were included for structured clinical re-evaluation and HLA typing (Figure 1).

On the basis of the mean reassessment score, 27 (21%) patients with suspected ABC-HSR were classified as clinically likely ABC-HSR (score ≥2), 43 (33%) as clinically unlikely ABC-HSR (score ≤2), and the remaining 61 (47%) patients as clinically uncertain ABC-HSR (Figure 1).

The scores of the two physicians were identical in 42% and differed by 1 point in 43% of cases. In 12% of cases, the score differed by 2 points and in the remaining 3% the score varied by >3 points.

Carriage of HLA-B*5701 and ABC-HSR

Approximately 6% of the 1,877 individuals starting ABC carried the HLA-B*5701 allele. This carriage rate was estimated from the overall prevalence of this genetic marker in 1,415 SHCS participants that were HLA-typed in research projects unrelated to drug HSR studies. Because this study was performed in the era preceding genetic screening, the prevalence of HLA-B*5701 carriage in the overall HLA-typed SHCS population (6%) should be representative for the population commencing ABC.

The proportion of HLA-B*5701-positive individuals was significantly higher in suspected ABC-HSR patients compared with ABC-tolerant controls (31% versus 1%, P<0.001; Figure 1). The structured clinical reassessment further strengthened the association between ABC-HSR diagnoses and carriage of HLA-B*5701 (Figures 1 and 2). Of the 27 individuals with likely ABC-HSR, 78% were HLA-B*5701-positive compared with only 5% of the 43 individuals with unlikely ABC-HSR (P<0.001).

The HLA-DR*0701 allele, which is in high linkage disequilibrium with HLA-B*5701 was significantly associated with likely ABC-HSR as compared with ABC-tolerant controls (23% versus 8%, P=0.01). No other HLA-B or HLA-DR alleles were significantly associated with ABC-HSR.

Carriage of HLA-B*5701 was strongly correlated with a higher classification score (OR 10.3 [95% CI 4.8–22.1] for physician 1 and 10.0 [95% CI 4.7–21.3] for physician 2, P<0.001 by ordered logistic regression for both calculations; Figure 3).

Frequency of symptoms related to ABC-HSR

In accordance with previous reports [11], fever and constitutional symptoms were more frequent in HLA-B*5701-positive compared with HLA-B*5701-negative individuals. Additionally, rash was slightly more frequent in HLA-B*5701-positive individuals (Figure 4).

Clinical and genetic characteristics of ABC-HSR in individuals with epicutaneous patch testing

Epicutaneous patch testing was performed in a subgroup of 23 individuals with presumed ABC-HSR. Four had a positive ABC patch test result, all of whom were HLA-B*5701-positive and were classified as likely HSR by both physicians (Figure 5). Two HLA-B*5701-positive individuals had negative patch test results. The remaining 17 individuals were HLA-B*5701-negative and had negative patch test results. In 14 (82%) of these patients, ABC-HSR was considered unlikely or uncertain.

Potential implications of genetic testing

On the basis of these results, it is estimated that genetic screening in the SHCS population would have prevented 31% (95% CI 23–40) suspected ABC-HSR reactions and 78% (95% CI 58–91) likely ABC-HSR reactions (Figure 1). Conversely, only 0.3% (95% CI 0.1–0.7) of HLA-B*5701-negative individuals exposed to ABC would have experienced a likely ABC-HSR. From the HLA-typed ABC-tolerant individuals, 2 out of 140 (1.4%) patients carried the HLA-B*5701 allele. ABC would therefore have been denied inappropriately in 1.3% (95% CI 0.2–5.0) of individuals starting ABC.

Re-exposure to ABC in individuals with suspected ABC-HSR

Our retrospective analyses identified five individuals with suspected ABC-HSR that were re-exposed to ABC during the study period because the treating physicians
retrospectively considered an ABC-HSR as unlikely. None of these individuals carried the HLA-B*5701 allele and none experienced an ABC-HSR upon reintroduction of ABC. The remaining 126 individuals were not re-exposed to ABC.

**Discussion**

The results of this study show that the diagnosis of ABC-HSR in a clinical routine setting can be refined using a structured clinical assessment and genetic testing. Of
Univariate and multivariate logistic regression analyses in human leukocyte antigen-typed individuals with abacavir hypersensitivity reactions (ABC-HSRs; n=131) versus ABC-tolerant controls (n=140). Carriage of the HLA-B*5701 allele was highly associated with the diagnosis of a suspected ABC-HSR (odds ratio [OR] 32.5, 95% confidence interval [CI] 7.7–137.9, \( P < 0.001 \)). The structured diagnostic reassessment strengthened this association (HLA-B*5701 carriage for likely ABC-HSR [OR 289.8, 95% CI 52.8–1,590.9, \( P < 0.001 \)]. Conversely, HLA-B*5701 carriage was not significantly associated with unlikely ABC-HSR (OR 3.45, 95% CI 0.47–25.3, \( P = 0.2 \)).

Figure 3. Diagnostic score after structured clinical reassessment in 131 individuals with suspected ABC-HSR

The bars show the proportion of abacavir hypersensitivity reactions (ABC-HSRs) with the respective classification score in HLA-B*5701-positive and HLA-B*5701-negative individuals. Carriage of HLA-B*5701 was strongly correlated with a higher classification score (\( P < 0.001 \) by ordered logistic regression). Scores ranged from +3 (ABC-HSR highly likely after diagnostic reassessment) to -3 (ABC-HSR highly unlikely after diagnostic reassessment).
Refining abacavir hypersensitivity diagnoses

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the 1,877 SHCS participants who started ABC between January 2000 and March 2005, 149 (8%) carried a diagnostic label of ABC-HSR. In accordance with current recommendations, the large majority (97%) of these individuals permanently discontinued ABC. However, when the 131 evaluable patients with suspected ABC-HSR were submitted to a structured clinical reassessment, 43 (33%) were considered unlikely to have experienced an HSR reaction, of whom only two carried the HLA-B*5701 allele. This proportion is similar to the ABC-tolerant control population. This finding suggests that a structured clinical assessment correctly identifies individuals at very low risk of an immunologically-mediated HSR reaction and indicates overdiagnosis of ABC-HSR in a clinical routine setting. Conversely, of the 27 patients with likely ABC-HSR, 78% carried the HLA-B*5701 allele, indicating that the majority of these patients were indeed drawn from a genetically-susceptible group. The sensitivity of the HLA-B*5701 allele for suspected ABC-HSR among Caucasians was slightly lower in our cohort as compared with a recent report by Saag et al. [11] (33% versus 44%).

A large proportion of suspected ABC-HSR patients remained in an uncertain diagnostic category after clinical review. Here, the high carriage rate of HLA-B*5701 (30%) compared with the background population frequency (6%), suggests an admixture of ‘true’ ABC-HSR individuals within the group. The diagnostic

Figure 4. Frequency of symptoms in 131 patients with suspected ABC-HSR

Figure 5. Patch test results, HLA-B*5701 carriage and structured clinical classification in 23 individuals who had stopped ABC because of suspected ABC-HSR

Patient | Patch test | HLA-B*5701 | ABC-HSR* |
--- | --- | --- | --- |
1 | + | + | + |
2 | + | + | + |
3 | + | + | + |
4 | + | + | + |
5 | - | + | + |
6 | - | + | +/- |
7 | - | - | + |
8 | - | - | + |
9 | - | - | + |
10 | - | - | +/- |
11 | - | - | +/- |
12 | - | - | +/- |
13 | - | - | +/- |
14 | - | - | +/- |
15 | - | - | +/- |
16 | - | - | - |
17 | - | - | - |
18 | - | - | - |
19 | - | - | - |
20 | - | - | - |
21 | - | - | - |
22 | - | - | - |
23 | - | - | - |

*Mean abacavir hypersensitivity reaction (ABC-HSR) reassessment score was either likely (+), uncertain (+/-) or unlikely (-). Patch test-positive and HLA-B*5701-positive (dark grey). Patch test-negative and HLA-B*5701-positive (light grey).
uncertainty might be attributed, to some extent, to incomplete case records and the challenges of retrospectively discriminating between multiple potential causative factors. The fact that the two independent physicians’ clinical diagnosis scores differed by ≥2 points in 15% of cases, even when applying stringent clinical criteria, illustrates the difficulties of confidently assigning or excluding a diagnosis of ABC-HSR on the basis of clinical assessment alone. Despite genetic screening, a substantial proportion of HLA-B*5701-negative individuals would remain in the uncertain diagnostic category. However, a thorough clinical assessment and monitoring guided by current guidelines should prevent premature ABC discontinuation in these individuals.

There are several potential sources for misclassification of ABC-HSR patients. Firstly, it is likely that the inherent level of diagnostic uncertainty, combined with an appreciation of the importance of ABC-HSR as a safety issue, has led many physicians to stop ABC without clear clinical evidence of an HSR. Secondly, patients themselves might stop ABC before consulting the treating physicians because of over-interpretation of minor symptoms. Thirdly, the symptoms of immunologically-mediated ABC-HSR might be missed initially. However, considering the progressive symptoms when continuing ABC in susceptible individuals, it appears unlikely that underdiagnosis of ABC-HSR is a widespread source of misclassification. The substantial proportion of HLA-B*5701-negative individuals with unlikely ABC-HSR labelled as HSR in this study further suggests that overdiagnosis rather than underdiagnosis of ABC-HSR is the main source of misclassification. It is also apparent from this retrospective study that the knowledge of the HLA-B*5701 status makes a considerable contribution to the assessment of ABC-HSR risk, as revealed in the regression analyses provided in Figure 2. Therefore, improved predictive tools (that is, HLA typing) and improved diagnostic approaches (that is, patch testing) should reduce the rate of misclassified ABC-HSR patients.

Although immunologically-mediated ABC-HSR appears to be clearly restricted to HLA-B*5701-positive individuals [5,11,12] and, in our study, the large majority of HLA-B*5701-negative individuals did not experience a clinically likely ABC-HSR, we can not exclude that severe reactions might also rarely occur in HLA-B*5701-negative individuals. These findings underscore the importance of maintaining a high level of clinical vigilance for ABC-HSR in all settings irrespective of genetic predisposition. Future multicohort studies should aim at recruiting HLA-B*5701-negative individuals with likely ABC-HSR, as thorough clinical, genetic and cellular analyses in these patients might uncover additional genetic markers and cellular mechanisms associated with ABC-HSR.

As in earlier studies, all individuals with positive patch tests carried the HLA-B*5701 allele [5,11,12]. However, two of six (33%) HLA-B*5701-positive individuals with suspected ABC-HSR had negative patch tests (one individual was classified as clinically likely and one as uncertain ABC-HSR; Figure 5). This finding is in line with a recent report [11], where negative patch test results were found in 15 of 57 (26%) White HLA-B*5701-positive individuals. Previous reports have shown that patch tests remain reactive for ≥6 years after HSR [11]. The two negative patch test results in HLA-B*5701-positive individuals (performed 32 and 37 months after HSR), therefore, can not be explained sufficiently by the timing of patch testing relative to ABC-HSR.

Fever and constitutional symptoms were more frequent in individuals carrying the HLA-B*5701 allele. This is in line with previous evidence that immunologically-mediated HSR reactions are characterized by increased proinflammatory cytokine levels [6]. However, this study was not able to identify specific major symptoms that could reliably discriminate ABC-HSR from non-specific symptoms beyond the standard diagnostic approach.

Detectable HIV RNA and more advanced HIV disease were associated with an increased risk for a diagnosis of suspected ABC-HSR. Low CD4+ T-cell counts and a faster progression of HIV disease have been associated with an increased risk HSR reactions to cotrimoxazole and nevirapine [13,14]. In a previous report involving >5,000 individuals exposed to ABC, the only factors associated with HSR in multivariate models were being treatment-naive when starting ABC and White ethnicity [15]. It remains to be determined which pathogenetic mechanisms confer the increased risk for ABC-HSR among individuals with detectible HIV RNA or more advanced HIV disease. Of note, the use of ABC in antiretroviral therapy-naive individuals did not explain the association of detectible HIV RNA with ABC-HSR (P=0.9; Table 1).

Our study has several limitations. Because of the retrospective design, non-specific symptoms associated with ABC-HSR might not have been recorded. Although we used standardized criteria for clinical diagnosis of HSR, the scoring remains subjective to some degree. Furthermore, the score and the cutoffs for the clinical reclassification were neither standardized nor validated. However, despite these limitations, the structured clinical reassessment considerably increased the correlation of the clinical ABC-HSR diagnostic classification with genetic susceptibility conferred by HLA-B*5701 carriage. In this study, historical diagnoses of ABC-HSR recorded within the SHCS were re-evaluated on the basis of a structured assessment of key clinical features. The process of revisiting and potentially refining ABC-HSR
diagnoses was based primarily on existing diagnostic criteria (supplemented by ABC patch testing in a minority of patients), and it is important to recognize that the results of HLA genotyping were not incorporated into this diagnostic strategy. This approach of revisiting previous ABC-HSR diagnoses is therefore somewhat removed from current pharmacogenetically-informed strategies (in which knowledge of HLA-B*5701 status is incorporated prospectively into risk assessment) and from individual physician-initiated review, which might incorporate direct knowledge of the initial syndrome as well as the ability to elicit patients’ recollections of these events. It has also to be acknowledged that the reclassification of ABC-HSR patients was performed by expert HIV physicians, whereas in clinical routine, the diagnosis sometimes relies on the clinical judgment of physicians less familiar with the specific components of the ABC-HSR syndrome. It is important to recognize that the process of reclassification was established for the purpose of this retrospective study and is not intended as a new instrument for the management of ABC-HSR patients. It is also important to acknowledge that genetic screening has been advocated for ABC-naive patients only, and has not been established as a basis for reconsidering cases previously labelled as ABC-HSR.

This retrospective study has revealed the potential for structured clinical assessment as well as HLA-B*5701 genetic screening and ABC patch testing to stratify individuals at high versus low risk for ABC-HSR. The study also confirms clinical trials data [7] indicating that overdiagnosis of ABC-HSR appears to be a widespread and inevitable consequence of the isolated use of clinical diagnostic approaches. In a previous study [8], we have shown that genetic screening programmes also reduce the rate of ABC discontinuation because of minor symptoms. Future studies should investigate whether combining genetic screening and a structured clinical assessment could reduce the rate of inappropriate ABC discontinuation without increasing the risk of severe ABC-HSR. The finding that even a retrospective review of patient charts improved the clinical classification of ABC-HSR illustrates the potential of an intensified training of the physicians prescribing ABC. Genetic screening programmes should therefore be complemented by an intensified training of physicians managing suspected ABC-HSR patients in order to reduce the rate of misclassified ABC-HSR. According to current guidelines, ABC re-exposure is contraindicated in all individuals previously labelled as ABC-HSR. It remains to be established whether reintroduction of ABC in HLA-B*5701-negative individuals with minor symptoms is feasible without increasing the risk for severe HSR. Until this issue has been clarified, reintroduction of ABC in individuals labelled as ABC-HSR has to be avoided irrespective of clinical symptoms or genetic susceptibility.

Our findings could have implications for the management of patients with suspected ABC-HSR in clinical routine. In settings where genetic screening is not available, the low risk of developing immunologically-mediated HLA-B*5701-restricted ABC-HSR in individuals with minor symptoms (that is, unlikely ABC-HSR) suggests that close clinical monitoring without immediate discontinuation of ABC is feasible without increasing the risk of severe HSR. In settings where genetic testing precedes the prescription of ABC, the recognition of the low risk for HLA-B*5701-negative individuals of developing clinically likely ABC-HSR could decrease the rate of inappropriate ABC discontinuation. A structured clinical assessment combined with genetic testing could enable a more confident prescription and discontinuation of ABC and could, therefore reduce both the rate of inappropriate ABC discontinuation and of severe ABC-HSR.

Acknowledgements

We thank the patients for their participation and the physicians and study nurses of all clinical centres for their excellent patient care.

Disclosure statement

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Additional file

An additional file listing the members of the Swiss HIV Cohort Study can be accessed via the Volume 13 Issue 8 contents page for Antiviral Therapy, which can be found at www.intmedpress.com (by clicking on ‘Antiviral Therapy’ then ‘Journal PDFs’).

References


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