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HLA-B*5701 and flucloxacillin associated drug-induced liver disease

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Conflicts of Interest—Dr S.A. Mallal has a financial interest in a patent for HLA-B*5701 testing to prevent abacavir hypersensitivity.
We read with interest the research letter by Jaime et al [1] which aimed to investigate whether flucloxacillin was associated with drug-induced liver injury (DILI) in HLA-B*5701 positive HIV patients. They did not identify DILI in any of their 10 HLA-B*5701 positive HIV-infected patients exposed to flucloxacillin for between 5 and 14 days. However, we submit that their observational cohort study did not have the power to either confirm or refute the recently reported association between flucloxacillin associated DILI and HLA-B*5701 (odds ratio = 80.6, \( P = 8.7 \times 10^{-33} \)) from a case-control study [2].

As shows in Table 1, true flucloxacillin DILI is an extremely rare disease with an estimated prevalence of 8.5/100 000 and the positive predictive value of HLA-B*5701 for flucloxacillin DILI is only 0.12%, meaning that almost 14000 white patients would need to be tested for HLA-B*5701 and excluded from flucloxacillin to prevent a single case of flucloxacillin DILI. This also means that at least 833 HLA-B*5701 positive individuals (or > 80 times the population, \( n = 10 \), reported in the study by Jaime et al. [1]) would have to be exposed to flucloxacillin, typically for more than 14 days, before identifying one who would develop flucloxacillin DILI. Furthermore, the number need to test to prevent one case is even higher in non-whites and populations of mixed ethnicity.

The feasibility of HLA screening to predict and prevent a serious drug reaction is related to the prevalence of the drug-related disease, the negative predictive value, the positive predictive value and the carriage frequency of the HLA allele in question in a specific population (Table 1) [3]. The 100% negative predictive value and 55% positive predictive value of HLA-B*5701 for abacavir hypersensitivity as well as the high prevalence of both abacavir hypersensitivity and the HLA-B*5701 allele in European populations explain a large part of why HLA-B*5701 screening could be translated into clinical practice [4]. In contrast to the 14 000 individuals that would need to be tested for HLA-B*5701 to prevent one case of flucloxacillin DILI, only 13 HIV-positive individuals would need to be tested to prevent one diagnosis of abacavir hypersensitivity (Table 1) [3].

There are other important arguments against avoiding flucloxacillin in HLA-B*5701 positive individuals. Flucloxacillin is the treatment of choice of serious methicillin sensitive Staphylococcus aureus (MSSA) infections in the UK and Australia, as it has superior bactericidal activity and efficacy and lower disease-related morbidity and mortality compared with alternatives such as vancomycin [5]. In view of this, a more pragmatic approach for HLA-B*5701 positive HIV patients with serious MSSA infections such as bacteremia, endocarditis or osteomyelitis, may be to initiate flucloxacillin with careful monitoring and consideration of their HLA-B*5701 status only if they develop biochemical evidence of hepatitis, at which point the drug can be stopped immediately.

We, therefore, suggest that, given the extremely small number of HLA-B*5701 positive patients treated with short-course flucloxacillin in this report, no statement about the safety of flucloxacillin
in HLA-B*5701 positive individuals can be drawn and, furthermore, that avoiding flucloxacillin in HLA-B*5701 positive HIV patients to prevent flucloxacillin DILI is neither feasible or recommended in clinical practice.

Table 1: Characteristics of HLA-B*5701 associated Abacavir Hypersensitivity and Flucloxacillin drug-induced liver injury.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>HLA Allele</th>
<th>HLA Carriage Rate</th>
<th>Prevalence of diagnosis</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
<th>NNT to prevent “1”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>B*5701</td>
<td>6-8% Caucasian, &lt;1% African/Asian, 2.5% African American</td>
<td>8% (includes 3% true HSR and 2-7% false positive diagnosis)</td>
<td>100% for patch test confirmed</td>
<td>55%</td>
<td>13</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>B*5701</td>
<td>As for abacavir</td>
<td>8.5/100,000</td>
<td>99.99%</td>
<td>0.12%</td>
<td>13819</td>
</tr>
</tbody>
</table>

DILI, drug-induced liver injury. Shows the number needed to test (NNT) to prevent one diagnosis of abacavir hypersensitivity or one case of flucloxacillin DILI, calculated from reference [2] and [4].
References


