Uncertainties of routine HLA B*5701 testing in black African HIV cohorts in the UK

S T Sadiq, M Pakianathan

Hypersensitivity reaction (HSR), associated with the antiretroviral abacavir, does not usually have serious outcomes unless recognised late or after rechallenge. Pharmacogenetic testing of human leucocyte antigen (HLA) B*5701 for HSR risk is being used increasingly in clinical practice backed by strong evidence among Caucasians and Hispanics.¹ In the Western Australian landmark studies, updated to improve diagnostic accuracy, positive predictive values (PPVs) and negative predictive values (NPV) of B*5701 for HSR were 78.9% and 99.4%,¹ respectively. When B*5701 screening was introduced into this cohort,² and in Brighton, UK,³ no HSRs were observed in 148 and 185 B*5701 negative patients, respectively, treated with abacavir.

However, associations between B*5701 and HSR have not been adequately investigated in black Africans who represent a substantial proportion of patients infected with HIV in the UK, perhaps resulting in the test being used in these populations without appreciation of screening effectiveness. The potential

problem is illustrated by estimations of "numbers needed to screen" summarised in table 1.

In Brighton, among the relatively small numbers from black (predominantly African) ethnicity, the B*5701 carriage rate was recently reported to be 5.3% (high for black Africans).³ However, as the molecular test used was unable to discriminate between HLA B*57 alleles, only one of the four black African patients designated B*5701 positive was truly positive by retrospective high-resolution DNA sequencing, giving a true carriage rate of 1.3%. The other three patients were positive for HLA B*5703, more commonly found in Africans.⁴ Assuming that the strong associations between B*5701 and HSR found in Caucasians apply to black Africans (table 1), a PPV of a B*5701-specific test for HSR in the African Brighton cohort would be 42.2%, equating to 182 black Africans being screened to correctly identify 1 at risk of HSR, and incorrectly identifying only 1.4. This compares with only 14 Caucasians being screened to identify 1 true case, with an incorrect

identification of 0.27. A substantial proportion of black African patients infected with HIV in the UK are Ugandan or Zimbabwean. The B*5701 carriage rate may be as high as 3% in Kampalan Ugandans,⁴ down to 0.4% among the Shona majority of Zimbabwe (http://www.allele frequencies.net). Using identical assumptions as above, PPVs for Kampalan Ugandans and Zimbabweans would equal 63.2% and 18.2%, equating to 53 and 1371 being screened to correctly identify 1 patient at risk of HSR, and incorrectly identifying 0.6 and 4.5, respectively. Although these numbers suggest a possible utility in some Ugandans (and then only if the association between B*5701 and HSR holds), testing as a whole might still be inappropriate given the low B*5701 carriage among Nilotic and Sudanic populations in Kenya,⁴ ethnic groups found in large proportions among Ugandans at our clinic. More sobering estimates are arrived at when considering results of a multicentre case-control study⁵ where case definitions were independently evaluated by doctors treating patients with HIV, who were blinded to the results, but where diagnostic criteria were not enhanced by epicutaneous patch testing as in Western Australia.¹ Using strict case definitions, a strong association between HSR and B*5701 was found in whites but not in a subset of black Americans, although the sample size could not exclude a weak association. Sensitivities and specificities for whites were 60% (lower than that found in other studies) and 96%, respectively, but for blacks 16% and 98%, respectively. Using these results for black Americans, the calculated PPVs for

Table 1 Calculated estimation of effectiveness of screening for human leucocyte antigen (HLA) B*5701 on different ethnic populations using two different measures of accuracy of HLA B*5701 for hypersensitivity reaction

Ethnic population† (sample size)	HLA B*5701 carriage rate (%)	Good accuracy of HLA B*5701 for HSR‡			Poor accuracy of HLA B*5701 for HSR§		
		PPV/NPV (%)	Numbers needed to screen to correctly identify one case	Numbers incorrectly denied abacavir for each patient correctly identified	PPV/NPV (%)	Numbers needed to screen to correctly identify one case	Numbers incorrectly denied abacavir for each patient correctly identified
Brighton cohort ³							
Whites (n=451)	8.6	83.9/99.4	14	0.2	NA	NA	NA
Black African (n=76)	1.3¶	42.2/99.9	182	1.4	9.5/98.8	807	9.5
Ugandan Kampalan* (n=161)	3	63.2/99.8	53	0.6	19.8/97.4	168	4
Kenyan Nandi/Luo* (n=240/ n=265)	0.8	30.9/100	404	2.2	6.1/99.3	2063	15.5
Zimbabwe Shona** (n=230)	0.4	18.2/100	1371	4.5	3.1/99.7	8031	31.1
Kenya Rural** (n=144)	0.3	14.3/100	2328	6	2.3/99.7	14 180	41.5

HSR, hypersensitivity reaction; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

Calculations for both scenarios are based on an assumption that B*5701 carriage rate reflects HSR incident rate.

†Only the Brighton cohort patients were specifically HIV-positive in the UK. All other populations were drawn from the general public from their respective countries in sub-Saharan Africa.

‡Sensitivity = 94.4%, specificity = 98.3% among largely Caucasian population.¹

§Sensitivity = 16%, specificity = 98% from black American population.⁵

*Rate takes into account false positives shown after retrospective DNA sequencing (see text).

**From <http://www.allele frequencies.net>.

Ugandans and Zimbabweans, 19.8% and 3.1%, respectively, correspond to 168 and >8000 patients being screened to correctly identify 1 patient at risk, and incorrectly identifying 4 and 31, respectively. Relating genetic test accuracies in black Americans to black Africans may seem speculative but, despite racial admixture in the black Americans, HLA B loci genetic distances are often shorter between them than between various black African populations.⁴

Despite biological plausibility for the role of B*5701 in the pathogenesis of HSR,¹⁻⁶ a lack of association in African populations may be explained by variation in genetic linkage to other critical genes involved, some known, others yet to be discovered. Indeed, HSR seems to be largely dependent on combinations of B*5701 with polymorphisms in the heat-shock protein Hom and tumour necrosis factor α genes as part of the ancestral 57.1 haplotype.¹

Given these uncertainties, how can apparent routine integration of B*5701 testing into clinical practice among black Africans be dealt with? The original Australian studies (and draft British HIV Association treatment guidelines, 2006) point out that B*5701 testing may be specific for Caucasians, and clinicians needed to maintain vigilance for HSR for all patients. Certainly, B*5701-specific tests should confirm positive results from non-specific ones. Cheap, accurate and rapid non-sequence-based typing methods able to do this are now becoming an available and attractive option.⁷ When the diagnosis of HSR is in serious doubt, a negative test for B*5701 with a negative epicutaneous patch test⁶ may be useful to guide safety of rechallenge, but more work is required to prove this. Although B*5701 screening is likely to be cost

effective in Caucasians,⁸ our calculations suggest that cost effectiveness for many black African populations is highly questionable. Furthermore, toxicities associated with alternative antiretroviral therapies make inappropriate denial of abacavir more relevant given the rare occurrence of severe HSR-related outcomes actually seen in current clinical practice. Therefore, in general, doctors should confidently prescribe abacavir to black African patients, provided adequate vigilance for HSR can be maintained, without testing for B*5701, until results of at least properly designed, perhaps ethnic-specific, case-control studies become available. Adequately powered prospective studies are unlikely to be practical given the prevalence rates. Implementation of such policies needs to take account of the lack of research in mixed populations and sensitivity around perceptions of discrimination.

Related to all this is the serious need for increased training of healthcare workers in understanding general concepts in genetics,⁹ so that as and when pharmacogenetic tests are introduced, counselling around them is appropriate and consistent. Although challenging, pharmacogenetic research in general needs to be proactive in recruiting diverse ethnic groups, in enough numbers from the outset, before introduction of routine clinical testing to avoid systematic discrimination in accessing new personalised medicine technologies.

ACKNOWLEDGEMENTS

We thank Professor Nick Carter (Genetics, St George's University of London) and Dr Andrew Copas (Medical Statistics; Royal Free and University College Medical School) for their comments.

Sex Transm Infect 2007;**83**:181–182.
doi: 10.1136/sti.2006.022335

Authors' affiliations

S Tariq Sadiq, St George's University of London, London, UK

M Pakianathan, St George's Healthcare NHS Trust, London, UK

STS wrote the manuscript and MRP contributed to it.

REFERENCES

- 1 **Martin A**, Nolan D, Gaudieri S, *et al*. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci USA* 2004;**101**:4180–5.
- 2 **Rauch A**, Nolan D, Martin 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.
- 3 **Reeves I**, Churchill D, Fisher M. Screening for HLA-B*5701 reduces the frequency of abacavir hypersensitivity reactions. *8th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*, 24–26 September 2006, San Francisco, California, USA (abstract 14). <http://www.intmedpress.com/lipodystrophy/webcasts/session4cfm> (accessed 16 Dec 2006).
- 4 **Cao K**, Moormann AM, Lyke KE, *et al*. Differentiation between African populations is evidenced by the diversity of alleles and haplotypes of HLA class I loci. *Tissue Antigens* 2004;**63**:293–325.
- 5 **Hughes AR**, Mosteller M, Bansal AT, *et al*. CNA30032 Study Team. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some but not all populations. *Pharmacogenomics* 2004;**5**:203–11.
- 6 **Phillips EJ**, Wong GA, Kaul R, *et al*. Clinical and immunogenetic correlates of abacavir hypersensitivity. *AIDS* 2005;**19**:979–81.
- 7 **Martin AM**, Nolan D, Mallal S. HLA-B*5701 typing by sequence-specific amplification: validation and comparison with sequence-based typing. *Tissue Antigens* 2005;**65**:571–4.
- 8 **Hughes DA**, Vilar FJ, Ward CC, *et al*. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics* 2004;**14**:335–42.
- 9 **The Royal Society**. Personalised medicines: hopes and realities. *Report* September 2005.