

Pharmacogenetics and clinical characteristics of patch test confirmed patients with abacavir hypersensitivity

Elizabeth Phillips, MD, FRCPC
BC Centre for Excellence in HIV/AIDS
Vancouver, British Columbia, Canada

Abacavir Hypersensitivity Syndrome (ABC HSR)

- ABC HSR occurs in 5% overall starting drug
- Presents with multiple symptoms & signs (fever, GI, cutaneous, respiratory)
- Usually present within the first 6 weeks (median 9-11 days)
- Pathogenesis is likely combination of immune, genetic and metabolic factors
- Strong association with HLA-B*5701* which may be valuable screening tool
- Rechallenge in patients “labeled” with ABC HSR is considered to be contraindicated

*Mallal S Lancet 2002; Hetherington S Lancet 2002, Rauch A, CID 2006 (in press)

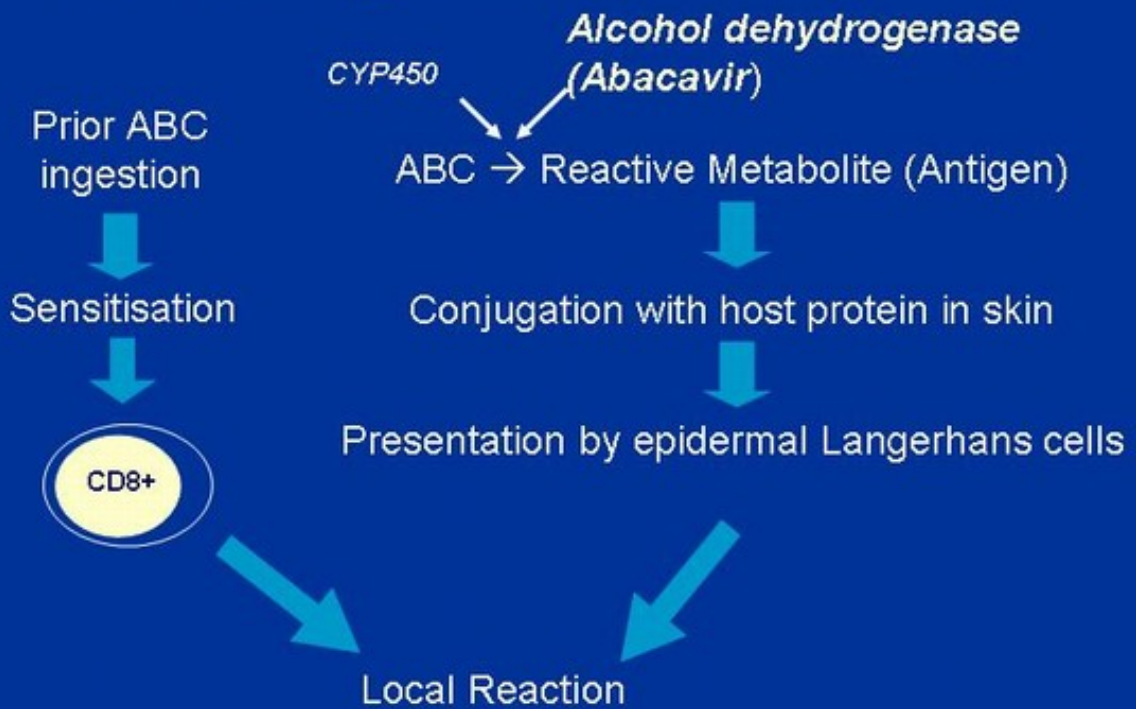
Abacavir HSR: Difficult to “phenotype”

- Major reason for stopping abacavir early (< 6 weeks) is concern re: HSR
- Clinical diagnosis can be imprecise and results in 2-3% false positive rate even in controlled clinical settings
 - Patients on concurrent drugs (eg. NNRTI, amprenavir)
 - Concurrent illnesses such as viral disease or immune restoration

Abacavir Patch Testing

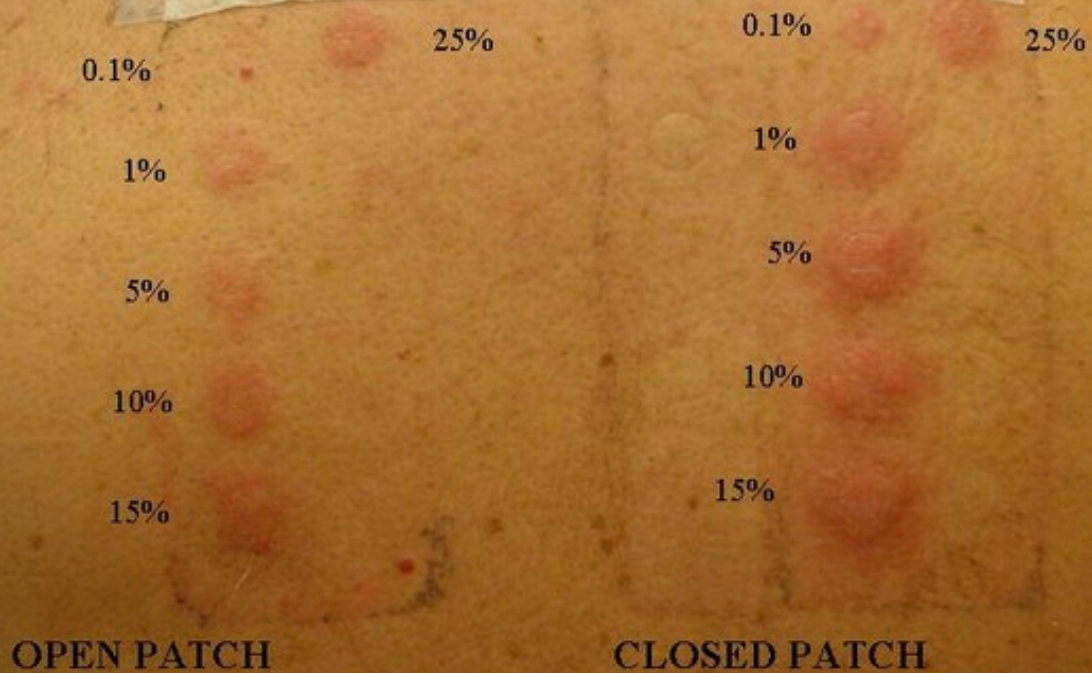
- Suggested to be sensitive, specific and durable in patients for the diagnosis of ABC HSR in patients with previous exposure to ABC
- Histopathology of patch test biopsy matches that of rash associated with ABC HSR (vigorous CD4+CD8+ response)
- Local cutaneous reactions only (no patients to-date with systemic complaints)
- Good correlation between patch test positivity and the genetic marker HLA-B*5701

Patch testing following ABC exposure



ABACAVIR POSITIVE PATCH:

Concentration Response



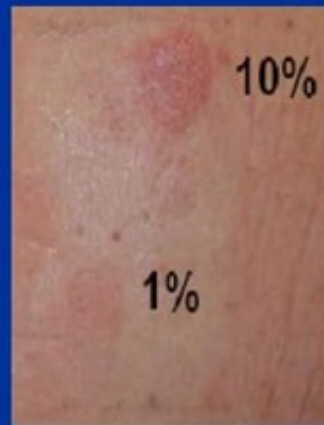
Methods

- Patients identified from Vancouver, Toronto, Perth, Switzerland with clinical label of ABC HSR
- Patch testing was performed with 1% and 10% ABC and petrolatum control and read at 24 hours
- HLA typing performed on consenting patch test positive and negative patients
- Patients with positive and negative patch tests were compared for clinical (time to onset of symptoms and number of symptoms) and genetic characteristics (HLA-B*5701)
- Subset of HSR, patch test positive patients were examined for polymorphisms in alcohol dehydrogenase 1 C and compared with a preexisting cohort of ABC tolerant patients

Patch Testing to 1% and 10% ABC



Negative

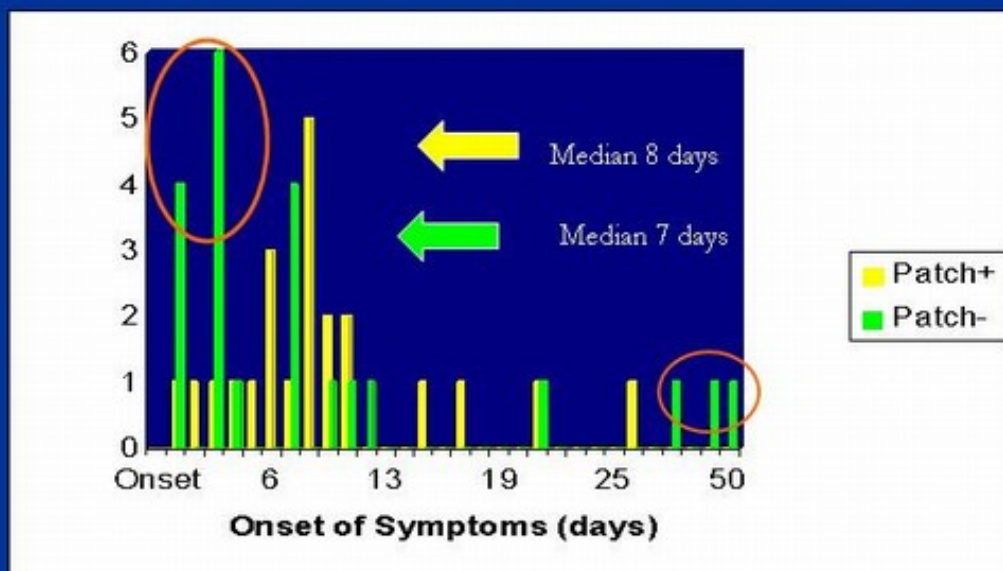


Positive

Results

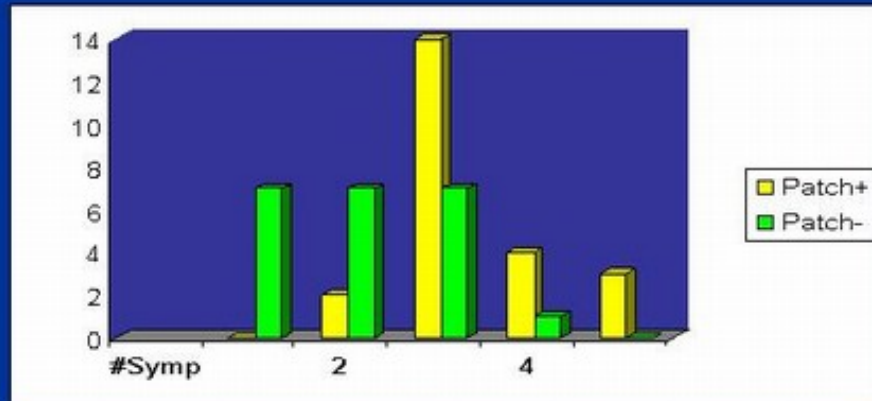
- 23 patch test positive and 23 patch test negative patients identified
- Patients did not differ according to demographic data at the time of patch testing such as age, gender, immunologic status, time since ABC HSR
- Positive patch tests occurred from 3 weeks to 5.3 years post ABC HSR and median time to testing between groups similar (2.5 years)

Onset to Symptoms of ABC HSR



*Range of onset of symptoms is represented more highly at the extremes of time (i.e. 1 day of treatment and >3 weeks of treatment) in the patch test negative patients

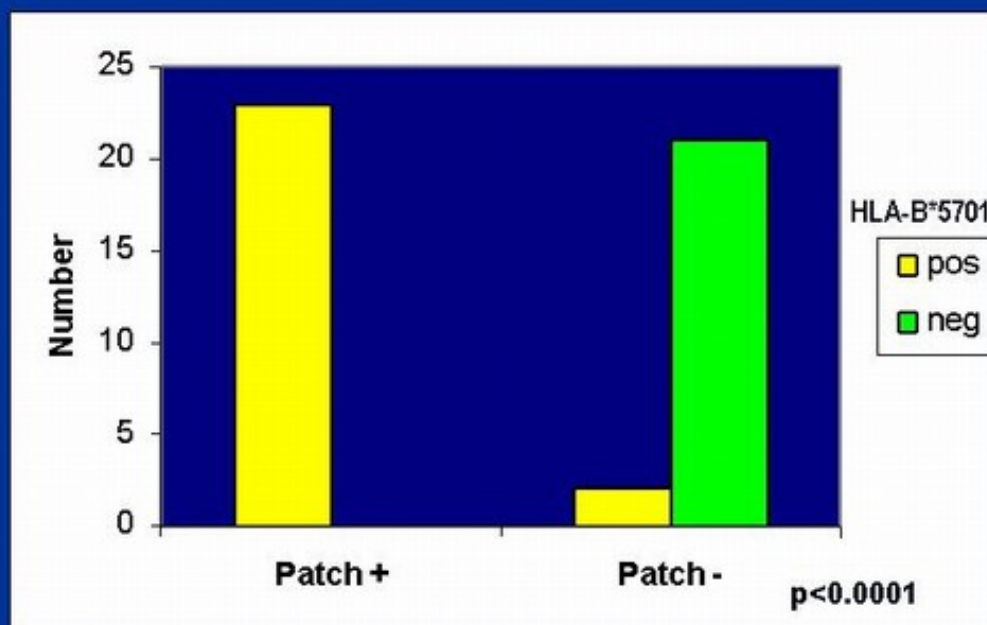
Number of Potential HSR Symptoms



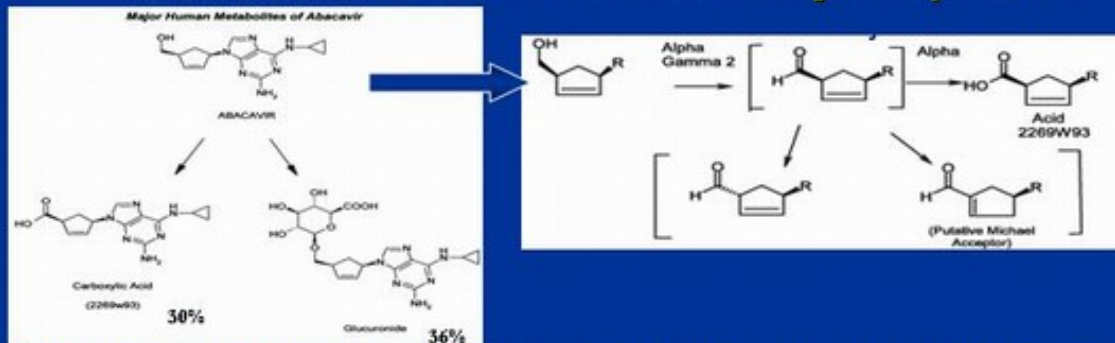
- 95.7% of patch test positive patients had > 2 symptoms versus 36.4% of patch test negative patients

- Patch test negative patients were significantly more likely to have experienced a total of < 2 symptoms

HLA-B*5701 According to Patch Test



Abacavir Metabolism and ADH Polymorphisms



¹Abacavir metabolism is mediated by alcohol dehydrogenase (ADH) Class I isozymes (A and C)

• ²Variants alleles of ADH encode enzymes that metabolise ethanol at different rates

• ²*ADH1C*349Ile* encodes an enzyme that rapidly metabolises ethanol

• ²*ADH1C*349Val* encoded enzyme has a lower activity in metabolising ethanol

¹Adapted from Walsh J. *et al. Chem Biol Interact* 2002; 142(1-2): 135-154

²Osler M. *et al. Am J Genet* 1999; 64: 1147-1157

Aim

Determine the distribution of the ADH1C A349G (Ile349Val) allelic polymorphism

Method

The ADH1C A349G (rs698) polymorphism was assessed by Taqman 7900 allele discrimination technology in patch test positive patients with a history of HSR and abacavir tolerant controls

Distribution of ADH1C A349G

	AA	AG	GG
HSR+/HLA-B*5701+ (Patch Test confirmed) (n=15)	3 (20.0%)	4 (26.7%)	8 (53.3%)
HSR-/HLA-B*5701+ (n=5)	3 (60.0%)	2 (40.0%)	0
HSR- (n=211)	94 (44.5%)	92 (43.6%)	25 (11.8%)

Conclusions

- Patch test positive and negative patients who have been labeled with ABC HSR differ in clinical characteristics and in particular time to first onset of symptoms (very early (day 1) and late onset (> 3 weeks) are overrepresented in patch negative) and patch test negative have significantly fewer number of symptoms.
 - Patch testing may be useful to refine the clinical case definition of ABC HSR
- All patch test positive patients in this study were HLA-B*5701 positive supporting the robustness of this association
- Patch confirmed patients with ABC HSR differ in the distribution of ADH1C A349G and particularly intriguing is the lack of this polymorphism in a group of HLA-B*5701 positive abacavir tolerant patients suggesting further research is warranted
 - Can metabolic factors protect against HSR?

Acknowledgements

■ Vancouver

- Marianne Harris
- Julio Montaner

■ Perth

- Coral-Ann Almeida
- Simon Mallal
- Annalise Martin
- David Nolan

■ Switzerland

- M. Cavassini
- Andri Rauch
- C. Thurnheer

■ Toronto

- Sandra Knowles
- Neil Shear

■ Canadian Dermatology Foundation

■ Canadian Association For AIDS Research