Characteristics of Abacavir Hypersensitivity Diagnoses According to *HLA-B*5701* Status and Subsequent Abacavir Patch Test Result

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Introduction

- Hypersensitivity (HSR) to abacavir (ABC) occurs in approximately 5-8% of patients, usually within the first 6 weeks of treatment, and necessitates immediate and permanent ABC discontinuation.[1]
- Clinical presentation is non-specific and involves combinations of symptoms from several categories of organ involvement (fever, skin rash, gastrointestinal [GI], constitutional, respiratory, etc).
- A high degree of HSR over-diagnosis has been observed, with rates of 2–7% reported in patients not receiving ABC in blinded comparative studies of ABC-containing products.
- ABC HSR is strongly linked to carriage of the major histocompatibility complex Class I allele *HLA-B*5701*.[2,3]
- Epicutaneous patch testing (EPT) has been used as a research tool to confirm immunologically mediated ABC reactions in subjects with a previous clinical diagnosis of HSR.[4]
- Assessing the characteristics of ABC HSR diagnoses according to *HLA-B*5701* status and/or subsequent EPT result may help to refine the HSR phenotype.

Methods

- PREDICT-1 (CNA106030)[5] was a large, blinded multinational study that randomised 1956 ABC-naïve subjects 1:1 to receive prospective *HLA-B*5701* screening (screening arm) or to a control arm with retrospective *HLA-B*5701* assessment at study end.
- *HLA-B*5701* positive subjects in the screening arm did not receive ABC in the study. All others received an abacavir-containing regimen for 6 weeks with investigators and patients blinded as to study arm
- Subjects with a clinical diagnosis of ABC HSR returned for EPT visits 6–10 weeks after drug discontinuation.
- Clinically diagnosed HSR during the observation period and clinically diagnosed HSR with a positive EPT result were the two co-primary endpoints of the study.
- Post-hoc exploratory analyses were undertaken to assess the relationship between HSR symptoms and *HLA-B*5701* status, EPT status, introduction of a new NNRTI and use of a concomitant PI using a Fishers exact test.

Results

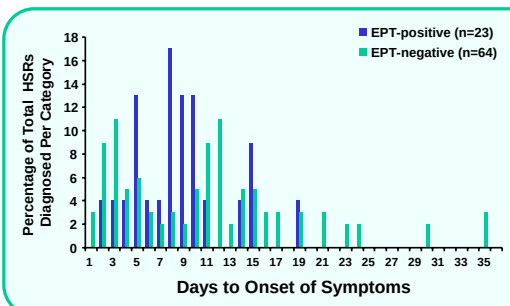
Table 1. *HLA-B*5701* Status and EPT Results in Subjects with Clinically Diagnosed ABC HSR

	Control arm	Screening arm	Total
Subjects with clinical HSR diagnosis	66	27	93
Subjects with clinical HSR diagnosis who were *HLA-B*5701* positive	30	0	30
Subjects with clinical HSR diagnosis who underwent EPT*	61	26	87
Subjects with a clinical HSR diagnosis and a positive EPT result	23	0	23

*Six subjects with clinically diagnosed HSR did not undergo EPT for reasons of refusal (n=4), loss to follow-up (n=1) and failure to attend EPT visits (n=1). One of these six subjects was *HLA-B*5701*-positive.

- Of patients who had a clinical diagnosis of HSR, 32% (30/93) were *HLA-B*5701*-positive. All but one of these underwent an EPT.
- Positive EPT results were obtained in 26% (23/87) of cases tested.
- Six *HLA-B*5701*-positive subjects with a clinical HSR diagnosis gave a negative EPT result.
- All subjects with a positive EPT result were *HLA-B*5701*-positive.

Figure 1. Days to Onset of Symptoms for Clinically Diagnosed ABC HSR According to Subsequent EPT Result



- The median time to onset of HSR symptoms was 8 days [IQR 5-10] for diagnoses with a positive EPT result, versus 11 days [IQR 4-14.5] for those with a negative EPT result. No HSR diagnosis with a positive EPT result presented after day 19 of treatment.
- Similar results were observed for HSR diagnoses in *HLA-B*5701*-positive subjects versus those who were *HLA-B*5701* negative (median 8.5 days to onset [IQR 6-11] versus 10 days [IQR 3-14]).
- These differences were not statistically significant.

Figure 2. Summary of HSR Symptom Categories by Subsequent EPT Result

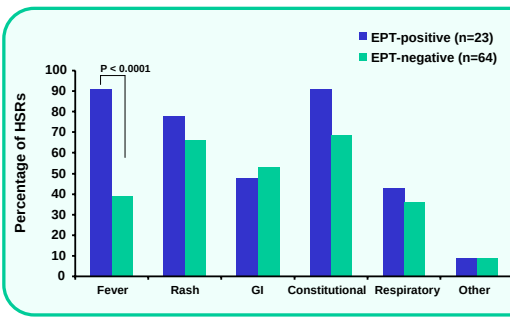
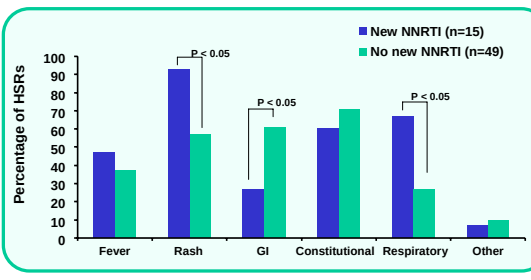


Figure 3: Combinations of HSR Symptom Categories by Subsequent EPT Result

	EPT-positive	EPT-negative
	Control arm N=23	Control and Prospective screening arms N=63
3 or More Categories	21 (91%)	37 (58%)
Rash Only	0	8 (13%)
GI and Constitutional	0	5 (8%)
Fever and Rash	2 (9%)	2 (3%)
Fever and Constitutional	0	2 (3%)
Rash and Constitutional	0	3 (5%)
GI Only	0	2 (3%)
Rash and Respiratory	0	2 (3%)
Fever and GI	0	1 (2%)
Constitutional and Respiratory	0	1 (2%)
Respiratory Only	0	1 (2%)

- Fever was present in 91% (21/23) of HSR diagnoses with a positive EPT result versus only 39% (25/64) of diagnoses that gave a negative EPT result (P < 0.0001).
- 91% (21/23) of HSR diagnoses with a positive EPT result involved symptoms from 3 or more categories, versus only 58% (37/64) of those without a positive EPT result (P = 0.0048).
- Amongst all HSR diagnoses that involved symptoms from 3 or more categories, fever with rash and constitutional symptoms were present with or without other symptoms in 65% (15/23) of diagnoses with a positive EPT result versus only 16% (10/64) of those without (P < 0.0001).
- Similar, but less compelling results were observed for HSR diagnoses in *HLA-B*5701*-positive subjects versus those who were *HLA-B*5701*-negative (Fever 80% [24/30] versus 40% [25/63]; P < 0.001. Three or more categories 83% [25/30] versus 57% [36/63]; P = 0.0208).

Figure 4: Impact of New NNRTI Initiation on Clinically Diagnosed HSR Symptoms in Subjects with a Negative EPT Result



- For HSR diagnoses that gave negative EPT results, rash and respiratory symptoms were significantly more common in those who initiated a new NNRTI during the study compared with those who did not (Rash: 93% [14/15] *versus* 57% [28/49]; P = 0.0158. Respiratory: 67% [10/15] *versus* 27% [13/49]; P = 0.0126). Conversely, GI symptoms were more common in those who did not initiate a new NNRTI (27% [4/15] *versus* 61% [30/49]; P = 0.0392)
- Similar trends were observed for HSR diagnoses in *HLA-B*5701*-negative patients who did or did not initiate a new NNRTI, although in these patients only the difference in respiratory symptoms reached statistical significance at the P < 0.05 level (60% [9/15] of those who took a new NNRTI versus 25% [12/48] of those who did not; P = 0.0308)
- No difference in GI symptom incidence was observed for EPT-negative HSR diagnoses in those who did or did not receive concurrent protease inhibitors during the study (data not shown)

Discussion

- All positive EPT results were obtained following a clinical diagnosis of HSR in subjects who were *HLA-B*5701*-positive.
- Of 29 *HLA-B*5701*-positive HSR diagnoses with EPT results, 23/29 gave a positive EPT result and 6/29 were EPT negative. It is not clear whether these six negative EPT results were due to operator error, initial clinical misdiagnosis of HSR or an intrinsic false-negative rate for the EPT procedure.
- This discordance cautions that while a positive EPT-result can confirm a prior immunologically mediated HSR event, a negative result cannot be used as confirmation that no HSR has occurred. For this reason, EPT was used in PREDICT-1 only to refine a statistical endpoint and not as a tool of patient management. ABC was not re-initiated in EPT-negative subjects.
- Time to onset of symptoms and the frequency distribution of these symptoms differed between clinical HSR diagnoses with a positive EPT result and those with a negative result. All HSR diagnoses with a positive EPT result showed onset of symptoms within 19 days of ABC initiation.
- HSR diagnoses in subjects who were *HLA-B*5701* positive and EPT positive tended to occur earlier and had a significantly higher incidence of fever and symptoms from at least three classes. These prospective findings are consistent with recent data from retrospective analyses in which EPT was used to refine HSR case ascertainment.[6,7] The high incidence of the combination of fever with rash and constitutional symptoms in cases with positive EPT results observed here has not been previously reported.
- For those HSR diagnoses with negative EPT results, the observation that rash occurred more in subjects taking a new NNRTI is consistent with the known confounding effect of NNRTI-associated rashes on HSR case ascertainment
- The significance of the higher incidence of respiratory symptoms also observed in these patients is uncertain.

Conclusions

- These clinical data from the PREDICT-1 study suggest that patients with immunologically mediated abacavir HSR, as evidenced by carriage of *HLA-B*5701* and a positive EPT result:
  - develop symptomatic HSR whose median onset occurs earlier (though not significantly so) and which presents within a shorter time period (within 3 weeks of abacavir initiation).
  - develop a presentation that is significantly more likely to involve fever and symptoms from at least 3 categories of organ involvement.
- However, overlap still exists between HSR symptom categories and time of onset for diagnoses between subjects with positive and negative EPT results, suggesting that refining the criteria for HSR case ascertainment based on these findings might reduce clinical over-diagnosis but would not eliminate it.
- This symptomatic overlap and the existence of six *HLA-B*5701*-positive clinical diagnoses of HSR without a positive EPT result underscores that avoiding ABC in prospectively screened, *HLA-B*5701*-positive individuals – as shown in PREDICT-1[5] – is likely to reduce HSR diagnosis and misdiagnosis more effectively than modifying the case ascertainment process.

References

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