Uptake of HLA-B*5701 Screening and Its Impact on Clinically Suspected Hypersensitivity Reaction to Abacavir in the OPERA® Observational Database

Karam Mounzer[1], Ricky Hsu[2], Cassidy Henegar[3], Jennifer Fusco[3], Vani Vannappagari[4], Chris Stainsby[5], Mark Shaefer[4], and Gregory Fusco[3]

[1]Philadephia FIGHT, Philadelphia, PA; [2]AIDS Healthcare Foundation, New York, NY; [3]Epividian, Inc., Durham, NC; [4]ViiV Healthcare, Inc., Research Triangle Park, NC; [5]GlaxoSmithKline, London, UK

BACKGROUND

- Early phase clinical trials identified a hypersensitivity reaction (HSR) associated with abacavir sulfate (ABC) use[1,2]
- ABC HSR is a multi-organ syndrome characterized by a sign or symptom in two or more of the following categories:
  - Group 1: Fever
  - Group 2: Rash
  - Group 3: Gastrointestinal (nausea, vomiting, diarrhea or abdominal pain)
  - Group 4: Constitutional (generalized malaise, fatigue, aches)
  - Group 5: Respiratory (dyspnea, cough, pharyngitis)[3]
- Following the identification of a genetic link between ABC HSR and a specific human leukocyte antigen allele, HLA-B*5701, a test was developed and entered clinical use in 2008 to identify those at risk for ABC HSR[4].

OBJECTIVE:

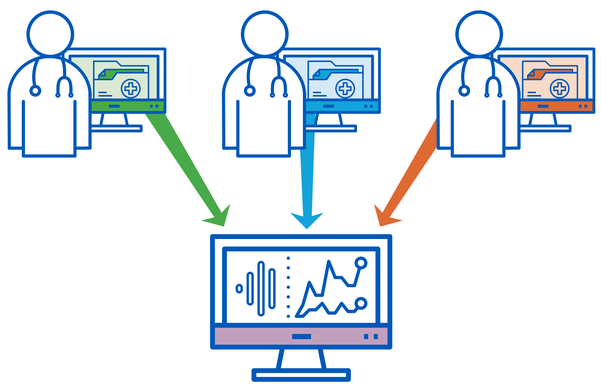
To assess the uptake and impact of HLA-B*5701 screening on the incidence of ABC HSR in real world practice

METHODS

Study Population

- Individuals in care in the OPERA database, an aggregation of electronic health record data from 79 clinics in 15 US states (Figure 1)
- HIV+ individuals initiating their first ABC-containing regimen between 01 January 1999 and 01 January 2016
- At least 13 years of age
- In continuous clinical care, at least one visit in the year prior and the year following initiation of ABC, with an OPERA care provider

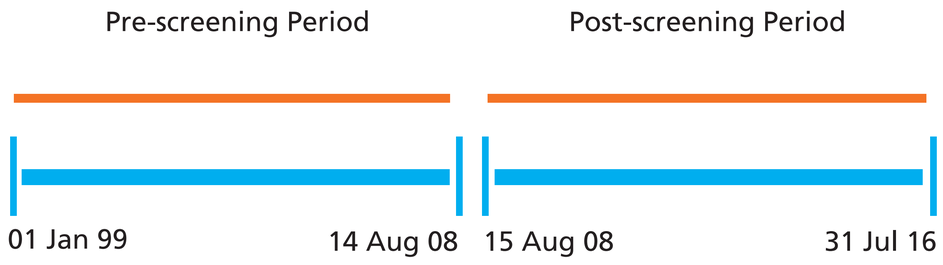
Figure 1. Electronic medical records from 79 clinics in 15 states make up OPERA



Study Design and Analysis

- Each patient was observed from regimen start until discontinuation of ABC, loss to follow-up, death, or data freeze (31 July 2016)
- Patient characteristics, HLA-B*5701 screening, and HSR events were assessed descriptively and compared by the screening period in which ABC was started for the first time (Figure 2)

Figure 2. HLA-B*5701 Screening Periods

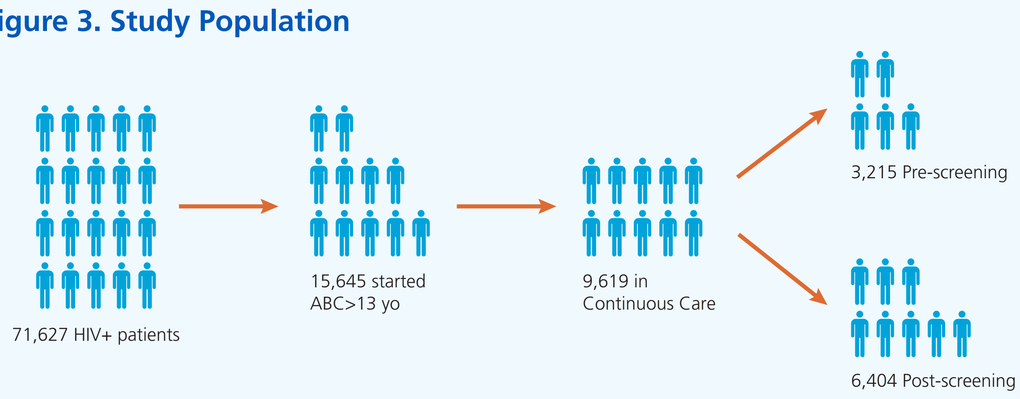


- Statistical comparisons were made using Pearson's chi-square or Fisher exact tests and Wilcoxon rank-sum tests. Incidence density was described using incidence rates and compared using incidence rate ratios.
- Events identified by diagnoses of HSR or symptoms of HSR within 6 weeks (42 days) of ABC initiation were adjudicated by a panel of physicians considering clinical information including symptomatology, potential confounders (such as concurrent medications), and event progression.

RESULTS

- One third of the study population (3,215), initiated abacavir in the pre-HLA-B*5701 screening period and two-thirds (6,404) in the post-HLA-B*5701 screening period. (Figure 3)

Figure 3. Study Population



Continuous care= at least one visit in the year prior and the year following initiation of ABC with an OPERA care provider Pre-Screening Period= 01 Jan 1999 to 14 Aug 2008
Post-Screening Period= 15 Aug 2008 to 31 July 2016

- Patients in the post-screening period were significantly different in demographic and clinical characteristics than those in the pre-screening period. (Table 1) These differences were consistent with the changing HIV epidemic during these time periods.

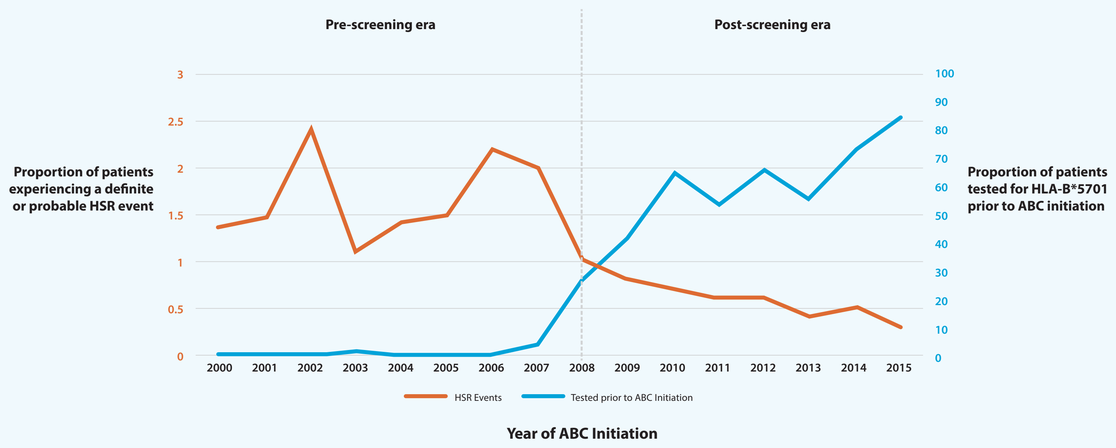
Table 1. Demographic and clinical characteristics by screening period at index

Characteristic (n, % or median, IQR)	Pre-Screening Period (n=3215)	Post-Screening Period (n=6404)	p-value
Age	40.4 (34.9, 46.4)	44.6 (34.6, 52.0)	**<0.0001**
Male Sex	2759 (86.5%)	5330 (83.3%)	**<0.0001**
African American	865 (26.9%)	2375 (37.1%)	**<0.0001**
MSM	1969 (61.2%)	3045 (47.5%)	**<0.0001**
Treatment Naive	1188 (37.0%)	2752 (43.0%)	**<0.0001**
Log RNA Viral Load	3.9 (2.2, 4.9)	2.1 (1.3, 4.5)	**<0.0001**
CD4 Count	274 (142, 452)	452 (270, 660)	**<0.0001**
AIDS Defining Illness	965 (30.0%)	959 (15.0%)	**<0.0001**

Pre-Screening Period= 01 Jan 1999 to 14 Aug 2008; Post-Screening Period= 15 Aug 2008 to 31 July 2016
MSM= Men who have sex with men

- Of patients initiating ABC in 2015 (the last full year of data), 84.3% were screened prior to ABC prescription, compared to 40% in 2008 after approval of the test. (Figure 4)

Figure 4. HLA-B*5701 screening and definite/probable HSR by year



- Using diagnoses of HSR or symptoms of HSR, 463 (4.8%) patients were identified for review (7.2% pre-screening period versus 3.5% post-screening period (p<0.0001)).
- Following adjudication rates fell to 2.8% pre-screening and 1.6% post-screening (p<0.0001).
- When these events were limited to those determined to be definite or probable, rates were further reduced to 1.6% pre-screening and 0.5% post-screening (p=0.0005).

Table 2. Incidence density rates of HSR by screening period compared by rate ratios

	HSR cases	Person-days on ABC	IR[1] (95% CI)
Any HSR[2]			
Pre-screening period[3]	51	129,856	39 cases / 100,000 p-d (30, 52)
Post-screening period[4]	37	232,905	16 cases / 100,000 p-d (12, 22)
Post-vs. pre-screening IRR (95% CI)[5]			**0.36 (0.23, 0.55)**
Definitive/Probable HSR[6]			
Pre-screening period	42	129,856	32 cases/ 100,000 p-d (23, 44)
Post-screening period	27	232,905	12 cases / 100,000 p-d (8,17)
Post-vs. pre-screening IRR (95% CI)	-----	-----	**0.31 (0.19, 0.52)**

[1]IR=Incidence rate with 95% confidence interval [2]Any HSR=Definite, probable and possible diagnoses
[3]Pre-Screening period=01 Jan 1999 to 14 Aug 2008 [4]Post-Screening period=15 Aug 2008 to 31 July 2016
[5]IRR=Incidence rate ratio with 95% confidence interval [6]Definite/Probable HSR=Definite and probable diagnoses only; p-d=person-days

CONCLUSIONS:

- HLA-B*5701 screening has increased steadily from its introduction in 2008.
- HSR events have decreased significantly since the introduction of the HLA-B*5701 test into clinical care in the United States.
- Screening of all patients prescribed ABC has not yet been achieved and rare cases of ABC-HSR still occur, suggesting continued education on the benefits of HLA-B*5701 screening is needed.

REFERENCES

1. Vilar FJ, Naisbitt DJ, Park BK, Pirmohamed M. Mechanisms of drug hypersensitivity in HIV-infected patients: the role of the immune system. J HIV Ther 2003; 8 (2): 42-7.
2. Vyakarnam A, King D, Tomkins S, Easterbrook P, Raffi F, Thurmond L, Thorborn D, Kemeny M. Immunological components of hypersensitivity to abacavir. 8th European Conference on Clinical Aspects and Treatment of HIV Infection, Athens, October 28-31, 2001. Abstract # 332.
3. Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, Lafon S, Pearce G, Steel H. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther 2001; 23 (10): 1603-14.
4. Mallal S, Phillips E, Carosi G, et. al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med 2008;358:568-79.

Support: This research was funded by ViiV Healthcare

ViiV Healthcare

Epividian®