

Frequency of Abacavir Hypersensitivity Reactions (HSR), Rechallenge Reactions, and HSR-Attributable Outcomes are Similar with the Use of Ziagen or Trizivir: Final Results from the Trizivir Epidemiology Study

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Introduction

Trizivir® Tablets (abacavir, lamivudine, and zidovudine; ABC/3TC/ZDV) were approved in the United States on November 14, 2000.

Multiple approved abacavir-containing products introduced the possibility that patients with a history of hypersensitivity-like events (HSR-LE) to one product containing abacavir may be rechallenged with another product containing abacavir.

To answer this question, the Trizivir Epidemiology Program Team conducted an epidemiologic study to examine the differences between ABC/3TC/ZDV and Ziagen® (abacavir, ABC) with respect to HSR-LE.

Methods

- Data were obtained from the Department of Veterans' Affairs Public Health Group, Ingenix, HIV Insight™, and CHORUS® databases.
- The study was powered to detect approximately 2.5-fold increase in risk of rechallenge associated with ABC/3TC/ZDV.
- Cases were identified from the observational databases and source medical records were reviewed to detail each case.
- Medical record information was abstracted for any patient with ABC discontinuation within 90 days of initiation associated with at least one event, condition, or symptom consistent with HSR.
- An Expert Medical Review Board adjudicated potential cases.
- Quality checks were implemented by pulling records at random to determine if case identification definitions were appropriate for each cohort.
- Frequency of HSR-attributable events, rechallenge, hospitalizations, and deaths were calculated.
- Relative risks of events for ABC and ABC/3TC/ZDV were assessed by Odds Ratios [OR] and 95% Confidence Intervals (CI) using ABC/3TC/ZDV as reference.
- Rechallenge was defined as "first exposure" to an ABC-containing treatment followed by ABC-sparing period(s), before a "last exposure" to an ABC-containing treatment.
- The denominator for HSR-LE was based on first exposure enumeration and the rechallenge denominator was based on enumeration of "last exposure".

Results

- First exposure to ABC was identified in 8877 patients and to ABC/3TC/ZDV in 2709, Total=11,856 (Table 2).
- HSR like events occurred in 3.6% (n=320) of patients first exposed to ABC and 3.1% (n=84) first exposed to ABC/3TC/ZDV, OR=1.17 (CI: 0.92, 1.49) (Table 2 and Figure 1).
- HSR-attributable hospitalizations occurred in 0.4% first exposed to ABC (n=33) and 0.4% to ABC/3TC/ZDV (n=10), OR=1.01 (CI: 0.5, 2.05) (Table 2).
- In the same 11,856 patients, last exposure was to ABC in 8724 patients and to ABC/3TC/ZDV in 2862 (Table 3).
- Rechallenge HSR cases occurred in 13 (0.1%) patients last exposed to ABC and 5 (0.2%) in ABC/3TC/ZDV, OR=0.85 (CI: 0.30, 2.39) (Figure 2).
- HSR-attributable rechallenge hospitalizations occurred in 4 (<0.1%) patients last exposed to ABC and 2 (0.1%) in ABC/3TC/ZDV, OR=0.66 (CI: 0.12, 3.58) (Table 3).
- No deaths were attributable to HSR.
- The Odds Ratio for HSR-like events comparing ABC to ABC/3TC/ZDV was 1.04 (95% CI: 0.80, 1.34) after adjusting for gender, age, ART experience and AIDS-defining illness.

Table 1. Usage Patterns of ABC and ABC/3TC/ZDV

Pattern	Number Ever Receiving Abacavir N=11586			
	n	%		
1. ABC only ¹	6936	59.9		
2. ABC/3TC/ZDV only ¹	2014	17.4		
3. ABC – ABC	878	7.6		
4. ABC – ABC/3TC/ZDV	69	0.6		
5. ABC/3TC/ZDV – ABC/3TC/ZDV	298	2.6		
6. ABC/3TC/ZDV – ABC	33	0.3		
7. Other patterns	1358	11.7		

¹Includes patients who eventually initiate another course of abacavir (either as ABC or ABC/3TC/ZDV), but only after successfully completing at least 90 days on the initial course.

Table 2. Summary of Initial Course of ABC and ABC/3TC/ZDV

Outcome	ABC First ¹ Exposure		ABC/3TC/ZDV First ¹ Exposure		Unadjusted Odds Ratio		
	N=8877		N=2709		95% CI		
	n	%	n	%	O.R.	L.L.	U.L.
Data unavailable	46	0.5	11	0.4	NA	NA	NA
Abstracted & evaluated	755	8.5	201	7.4	NA	NA	NA
HSR-like event	320	3.6	84	3.1	1.17	0.92	1.49
HSR-like hospitalization	33	0.4	10	0.4	1.01	0.5	2.05
HSR-like death	0	0.0	0	0.0	NA	NA	NA

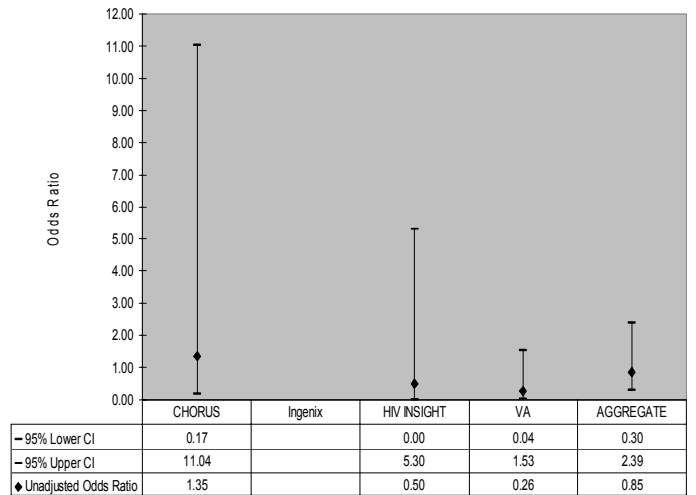
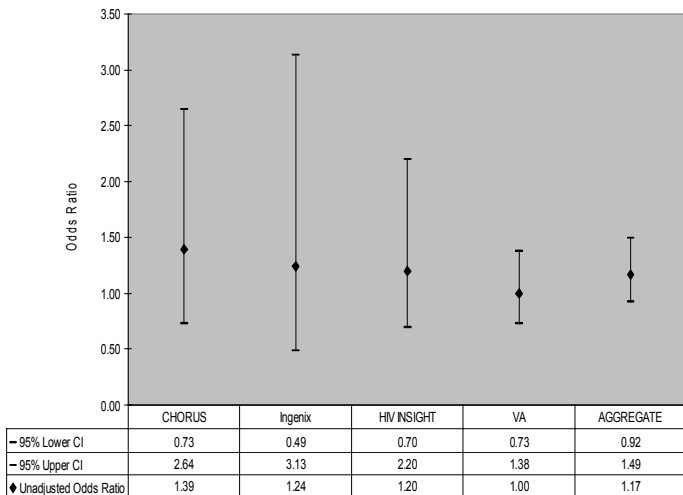
¹ABC and ABC/3TC/ZDV exposure groups are mutually exclusive; classification is based on Table 1. Groups 1, 3, 4 and part of 7 constitute the "ABC First Exposure" group. Groups 2, 5, 6 and part of 7 constitute the "ABC/3TC/ZDV First Exposure" group.

Table 3. Summary of Final Course of ABC or ABC/3TC/ZDV

Outcome	ABC Last ¹ Exposure		ABC/3TC/ZDV Last ¹ Exposure		Unadjusted Odds Ratio		
	N=8724		N=2862		95% CI		
	n	%	n	%	O.R.	L.L.	U.L
Rechallenge HSR	13	0.1	5	0.2	0.85	0.30	2.39
Rechallenge HSR hospitalization	4	0.0	2	0.1	0.66	0.12	3.58
Rechallenge HSR death	0	0.0	0	0.0	NA	NA	NA

Figure 1. Possible/Probable/Definite HSR-like Event Unadjusted Odds Ratio and 95% CI; ABC compared to ABC/3TC/ZDV

Figure 2. Possible/Probable/Definite Rechallenge HSR Unadjusted Odds Ratio and 95% CI, ABC compared to ABC/3TC/ZDV



Discussion

Study Strengths:

This study was a novel component of the overall risk management program for ABC containing products.

The study used robust methodology for case ascertainment.

A conservative, consensus-based approach for case screening and adjudication by an independent panel of experts resulted in identification of the events of interest.

The study design allowed for addressing study questions within a broad array of HIV-infected patients and health care settings in the United States.

The number of events of abacavir HSR, abacavir HSR rechallenge, HSR-related hospitalization, and HSR-related deaths were relatively low.

Although there were fewer events than expected when the study was designed, there was no indication of any meaningful differences between the ABC and ABC/3TC/ZDV groups.

Study Weaknesses:

Differences may exist between ABC and ABC/3TC/ZDV with respect to the outcomes evaluated; however these could not be detected due to the low numbers of events observed in this large population.

Conclusion

- **No differences were observed between ABC and ABC/3TC/ZDV in any of the outcomes studied.**
- **Of the 11,586 abacavir users included in the Trizivir Epidemiology Study, there was an overall percentage of HSR-like events between 3.1 and 3.6.**
- **Few hospitalizations attributed to HSR-like events were observed in this study.**
- **Rechallenge HSR events were uncommon in both ABC and ABC/3TC/ZDV treatment groups.**
- **The risk of rechallenge was similar for ABC/3TC/ADV and ABC alone.**
- **No deaths attributable to HSR or to rechallenge HSR-like events were observed in the ABC or ABC/3TC/ZDV groups.**

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