# Resistance Profile after Treatment with an Atazanavir-Containing Regimen: First Interim Analysis Results from the IMPACT Study (BMS AI424-128)

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## BACKGROUND

- During early clinical studies of atazanavir (ATV), a unique resistance profile was elucidated: treatment-naïve patients treated with ATV who developed viral failure with protease inhibitor (PI) resistance did so only in the presence of the I50L substitution in the protease gene of HIV. This substitution distinguishes the resistance profile of ATV from the resistance profiles of all other currently marketed PIs. A study of clinical isolates has shown that, rather than creating resistance across the PI class, the emergence of I50L actually increases or maintains the susceptibility of HIV to some other PIs.[1] Hence, failure of an initial ATV-based regimen may preserve future treatment options.
- Now that combining ATV with another PI, ritonavir (RTV), for pharmacokinetic enhancement is common in highly active antiretroviral therapy (HAART) regimens, it has become increasingly important to understand the implications of the I50L substitution. Currently, there are limited clinical data describing the emergent viral resistance patterns in patients who fail first-line therapy with a HAART regimen that contains ATV and low-dose RTV.[2]
- In September 2004, BMS Study AI424128 was initiated to evaluate the I50L substitution in patients who experienced virologic failure while on an ATV-containing HAART regimen. Results from the first planned interim analysis of the data are presented here.

## RESEARCH HYPOTHESIS

- **Research Hypothesis:** In patients experiencing virologic failure while receiving ATV-containing HAART regimens, the prevalence of the I50L substitution is lower in patients treated with atazanavir/ritonavir (ATV/r) compared with those treated with ATV without RTV.

## OBJECTIVES

**Primary Objective:**

- To compare the prevalence of the I50L substitution in viral isolates from patients virologically failing ATV-containing HAART regimens with the I50L substitution prevalence in patients failing ATV/r-containing HAART regimens, regardless of prior treatment history.

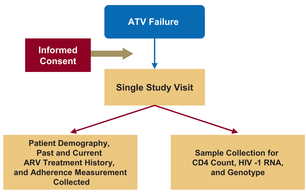
**Key Secondary Objectives:**

- To determine the overall prevalence of the I50L substitution in patients failing ATV-containing HAART regimens.
- To compare the prevalence of the I50L substitution in patients failing ATV/r as a first PI-containing regimen versus patients failing ATV/r as a second or later PI-containing regimen.
- To compare the prevalence of the I50L substitution (regardless of RTV combination) in patients failing ATV as a first PI-containing regimen vs. patients failing ATV as a second or later PI-containing regimen.
- To determine if the I50L substitution is associated with nucleoside reverse transcriptase inhibitor (NRTI) substitutions.

## METHODS

- Multicenter, cross-sectional study of HIV-infected treatment-experienced patients who have experienced virologic failure while on an ATV-containing HAART regimen.
- Enrollment is planned at international sites over 5 years but this first of yearly interim analysis contains data from 230 U.S. sites only.
- Yearly analyses and reporting of the prevalence of I50L will be done per study protocol due to the potential impact on clinical practice.
- Virologic failure (VF) is defined as either:
  - (1) a confirmed virologic rebound, defined as an HIV RNA by PCR ≥1000 copies/mL after achieving a value <400 copies/mL on at least two consecutive measurements (“**Rebounder**”)
  - or (2) an HIV RNA ≥1000 copies/mL after 24 weeks of ATV therapy (“**Non-Responder**”), who were further classified based on VL response to current ATV-containing therapy
  - In both cases, HIV RNA ≥1000 copies/mL must be confirmed by screening measurement performed within 14 to 90 days of the first qualifying HIV RNA value of ≥1000 copies/mL.

**Figure 1. Study Schema: AI424128**




## RESULTS

**Table 1. Patient Characteristics**

| | With I50L | | Without I50L | | Overall Total |
|---|---|---|---|---|---|
| | ATV | ATV/r | ATV | ATV/r | |
| **# Patients** | 3 | 9 | 21 | 95 | 128 |
| **Mean Age (yrs)** | 44 | 43 | 48 | 46 | 46 |
| **Male (%)** | 67 | 78 | 91 | 94 | 91 |
| **Race (%)** | | | | | |
| **White** | 33 | 44 | 52 | 57 | 55 |
| **Black** | 33 | 56 | 24 | 20 | 23 |
| **Hispanic** | 33 | 0 | 24 | 20 | 20 |
| **Asian** | 0 | 0 | 0 | 3 | 2 |
| **Mean Weight (kg)** | 79 | 83 | 75 | 76 | 76 |
| **CDC Stage C (%)** | 33 | 44 | 57 | 57 | 56 |
| **Duration (Median)** | | | | | |
| **HIV (years)** | 17 | 13 | 15 | 13 | 13 |
| **ATV (months)** | 24 | 17 | 16 | 16 | 16 |
| **CD4 (mean cells/mm$^3$)** | | | | | |
| **Nadir** | 108 | 117 | 167 | 98 | 111 |
| **@ Study Visit** | 283 | 247 | 276 | 209 | 225 |
| **HIV-1 RNA (median $\log_{10}$ copies/mL)** | | | | | |
| **@ ATV start** | 4.8 | 4.9 | 4.7 | 4.8 | 4.8 |
| **@ Study Visit** | 5.1 | 5.0 | 4.2 | 4.4 | 4.4 |

- Of 128 patients enrolled, 9.4% had I50L.
- Highly advanced population:
  - 50% CD4 <200 cells/mm$^3$
  - 55.5% CDC Stage C
  - 62.5% had HIV for 10$^+$ years
- Prevalence of I50L less in subjects on ATV/r vs. ATV
  - 9/104 (8.7%) on ATV/r vs. 3/24 (12.5%) on ATV

## RESULTS cont'd

**Table 2. Prevalence of I50L Mutation**

| Selected Patient Characteristics | n/N (%) | Odds Ratio (95% CI) |
|---|---|---|
| **Second or Later PI: First PI Use** | 12/116 (10%): 0/12 (0%) | N/A |
| **Duration of ATV Use (12-24 mo: <12 mo)** | 12/74 (16%): 0/38 (0%) | N/A |
| **Sex (Female: Male)** | 3/11 (27%): 9/117 (8%) | 4.50 (1.01, 19.99) |
| **Race (Black: White)** | 6/30 (20%):5/70 (7%) | 3.25 (0.91, 11.64) |
| **HIV-1 RNA @ Study Visit (≥10$^5$: <10$^5$) copies/mL** | 6/36 (17%): 6/92 (7%) | 2.87 (0.86, 9.57) |
| **Weight (≥80 kg: <80 kg)** | 6/50 (12%): 6/78 (8%) | 1.64 (0.5, 5.39) |
| **Duration of HIV Infection, yrs (11-20: <5)** | 8/75 (11%): 1/13 (8%) | 1.43 (0.16, 12.52) |
| **Nadir CD4 (≥200: <200) cells/mm$^3$** | 3/25 (12%): 9/103 (9%) | 1.42 (0.36, 5.70) |
| **Age (45-64: <45)** | 6/60 (10%): 6/65 (9%) | 1.09 (0.33, 3.59) |
| **CD4 @ Study Visit (≥200: <200) cells/mm$^3$** | 6/61 (10%): 6/64 (9%) | 1.05 (0.32, 3.47) |
| **Duration of HIV Infection, yrs (5-10: <5)** | 2/28 (7%): 1/13 (8%) | 0.92 (0.08, 11.2) |
| **Use of ATV/RTV: ATV** | 9/104 (9%): 3/24 (13%) | 0.66 (0.17, 2.66) |
| **Race (Hispanic: White)** | 1/25 (4%): 5/70 (7%) | 0.54 (0.06, 4.88) |

- Results for Women and Black race should be interpreted with caution due to small sample size.

**Table 3. Prevalence of I50L by PI Exposure**

| | Number of Patients with I50L (n=12) | Number of Patients without I50L (n=116) | Total (n=128) |
|---|---|---|---|
| **PI-Naïve** | | | |
| Failed on ATV or ATV/r as First PI Therapy, n (%) | | | |
| ATV | 0 | 3 (3%) | 3 (2%) |
| ATV/r | 0 | 9 (8%) | 9 (7%) |
| **PI-Experienced** | | | |
| Prior PI Therapy[a], n (%) | | | |
| Boosted | 7 (58%) | 88 (76%) | 95 (74%) |
| Unboosted | 5[b] (42%) | 16[c] (14%) | 21 (16%) |

a. Median duration of exposure to prior PIs 63 months.
b. One subject initially received ATV200 mg daily for 4 months but was switched to ATVr300/100 mg daily.
c. Two subjects initially received ATV400 mg daily but were switched to ATVr300/100 mg daily.

- Of the 12 patients (9.4%) who developed the I50L mutation, none were on initial PI therapy with ATV or ATV/r.
- Primary PI mutations, including I50L, were not seen at virologic failure in those patients who received initial PI-based therapy with ATV/r.
- Among PI-experienced patients, the prevalence of I50L was 10% (12/116).

**Table 4. Effect of Previous Therapy on Prevalence of I50L**

| Prior Antiretroviral (ARV) History | With I50L N=12 n (%) | Without I50L N=116 n (%) |
|---|---|---|
| **Prior PI Therapy (P=0.033)[a]** | | |
| Boosted PI | 7 (58.3) | 88 (75.9) |
| Unboosted PI | 5 (41.7) | 16 (13.8) |
| Never used PIs | 0 | 12 (10.3) |
| **Prior NRTI Therapy (P=0.837)** | | |
| None | 0 | 5 (4.3) |
| 1 NRTI | 1 (8.3) | 9 (7.8) |
| 2 NRTIs | 7 (58.3) | 73 (62.9) |
| 3 or more NRTIs | 4 (33.3) | 29 (25.0) |

a. P-value based on analysis of association of specific ARV history factor (eg Prior NRTI Therapy) with presence or absence or I50L substitution, considering all subcategories of factor (not a pairwise comparison).

- A lower prevalence of I50L was seen in patients who had prior exposure to boosted PIs, 7/95 (7.4%) vs. those who were exposed to an unboosted PI or never used a PI before, 5/33 (15.2%).
- Prior exposure to NRTIs did not appear to have an effect on the presence of I50L

## DISCUSSION

- Recent clinical studies have shown only isolated cases of emergence of PI resistance mutations in treatment-naïve patients failing on a boosted PI regimen. In this study, no patient on initial PI-based therapy with ATV/r was found to have primary PI resistance mutations, consistent with recently published data of a randomized trial of initial therapy comparing ATV with ATV/r (AI424-089).[3]
- Colonno et al previously described ATV resistance development in clinical studies AI424-009, AI424-043, and AI424-045 which enrolled PI-experienced patients. Resistance occurred via emergence of an I50L substitution in 30% (18/60) of the ATV and ATV/r isolates from treatment-experienced patients. The remaining 70% of isolates from PI-experienced patients treated with ATV or ATV/r developed resistance through alternative pathways involving substitutions commonly observed with other PIs.[4] The prevalence of I50L in this study of predominantly treatment-experienced patients likely reflects evolution of resistance through alternative pathways.

## CONCLUSIONS

- In this first interim analysis of a cohort of patients with virologic failure on an ATV-containing regimen, the overall I50L prevalence was 12/128 (9.4%).
- Early trends support the research hypothesis that the I50L substitution was less prevalent in patients treated with ATV/r than with ATV.
- Primary PI mutations, including I50L, were not seen at VF in patients on initial PI-based therapy with ATV/r.
- In PI-experienced patients, a lower prevalence of I50L was seen in patients who had prior exposure to boosted PIs as compared to unboosted PIs due to development of resistance through alternative pathways.
- Prior exposure to NRTIs did not appear to have an effect on the presence of I50L.

**Note that the results of this first interim analysis must be interpreted with caution since few patients took ATV or ATV/r as their initial PI therapy and the overall prevalence of I50L was low.**

## REFERENCES

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