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Low frequency of genotypic resistance in HIV-1-infected patients failing an atazanavir-containing regimen: a clinical cohort study

David I. Dolling[1]*, David T. Dunn[1], Katherine A. Sutherland[2], Deenan Pillay[3], Jean L. Mbisa[2], Chris M. Parry[4], Frank A. Post[5], Caroline A. Sabin[3] and Patricia A. Cane[2] on behalf of the UK HIV Drug Resistance Database (UKHDRD) and the UK Collaborative HIV Cohort Study (UK CHIC)†

[1]Medical Research Council Clinical Trials Unit, London, UK; [2]Virus Reference Department, Public Health England, London, UK; [3]Research Department of Infection, University College London, London, UK; [4]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [5]School of Medicine, Kings College London, London, UK

*Corresponding author. Tel: 020-7670-4933; E-mail: d.dolling@ctu.mrc.ac.uk
†For further details please see the Acknowledgements section.

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Objectives: To determine protease mutations that develop at viral failure for protease inhibitor (PI)-naive patients on a regimen containing the PI atazanavir.

Methods: Resistance tests on patients failing atazanavir, conducted as part of routine clinical care in a multicentre observational study, were randomly matched by subtype to resistance tests from PI-naive controls to account for natural polymorphisms. Mutations from the consensus B sequence across the protease region were analysed for association and defined using the IAS-USA 2011 classification list.

Results: Four hundred and five of 2528 (16%) patients failed therapy containing atazanavir as a first PI over a median (IQR) follow-up of 1.76 (0.84–3.15) years and 322 resistance tests were available for analysis. Recognized major atazanavir mutations were found in six atazanavir-experienced patients ($P < 0.001$), including I50L and N88S. The minor mutations most strongly associated with atazanavir experience were M36I, M46I, F53L, A71V, V82T and I85V ($P < 0.05$). Multiple novel mutations, I15S, L19T, K43T, L63P/V, K70Q, V77I and L89I/T/V, were also associated with atazanavir experience.

Conclusions: Viral failure on atazanavir-containing regimens was not common and major resistance mutations were rare, suggesting that adherence may be a major contributor to viral failure. Novel mutations were described that have not been previously documented.

Keywords: HIV, drug resistance mutations, naive patients, protease inhibitors, virological failure

Introduction

Since the approval of the protease inhibitor (PI) atazanavir by the FDA (and 'positive opinion' by the European Medicines Agency) in 2003 it has become a widely used third agent in combination antiretroviral therapy (ART) and is recommended as a possible component of first-line therapy in national and international HIV treatment guidelines.[1,2] Previous research investigating the development of drug resistance to atazanavir in a non-randomized controlled trial setting is limited by its focus on patients with prior PI exposure[3,4] or the development of major PI mutations.[5] Randomized controlled trials[6,7] have shown that the key substitutions in patients failing atazanavir-containing regimens are I50L and N88S.[7] This study examines patterns of resistance to atazanavir in a large clinical cohort of patients with no prior PI exposure.

Methods

Genotypic resistance test results of population sequencing of the *pol* gene were obtained from the UK HIV Drug Resistance Database (UKHDRD)[8] and linked to pseudo-anonymized clinical information from the UK Collaborative HIV Cohort Study (UK CHIC).[9] The UKHDRD and UK CHIC were established in 2001 and collect, respectively, all resistance tests conducted at public laboratories within the UK as part of routine clinical care, and clinical information routinely collected on HIV-positive individuals aged over 16 years who have attended one of the 15 collaborating centres for care at any time from 1996.

Patients who were PI naive, regardless of other ART experience, and who were initiated on a regimen containing atazanavir between 2001 and 2010 were included for analysis in the study. Virological failure was defined as: (i) two consecutive viral loads >1000 copies/mL after previous suppression (≤400 copies/mL); (ii) one viral load >1000 copies/mL after previous suppression followed by a treatment change; or (iii) one viral load >1000 copies/mL after 180 days on ART without suppression. Valid resistance tests were samples taken after at least 30 days of atazanavir treatment and within 30 days of discontinuing the drug. Where more than one resistance test was available for a patient, the latest test was selected for analysis. For each index resistance test we attempted to select at random 10 resistance tests from ART-experienced, PI-naive patients with the same viral subtype as controls for variation in background polymorphisms. When fewer than 10 such tests could be identified they were supplemented by tests from ART-naive patients with the same viral subtype. For rare subtypes such as CRF11 and CRF13 (where CRF stands for circulating recombinant form), sufficient control samples to match in a 1:10 ratio were not available. Apart from these factors, control samples were selected stochastically and no other demographic information was used in the process.

Protease mutations were categorized based on the IAS-USA 2011 mutation list as either major or minor atazanavir mutations.[10] The prevalence of each amino acid substitution was compared between index and control resistance tests using Fisher's exact test. Mutations are reported if they are: (i) classified as a major atazanavir mutation or (ii) observed in at least two index resistance tests and with a significantly ($P<0.05$) higher frequency compared with control tests. Subtype was inferred from the *pol* sequence using the REGA subtyping algorithm.[11] No adjustments were made for the multiple hypothesis tests performed, on the basis that this is an exploratory analysis to identify associations to be verified in other datasets. All analyses were conducted in Stata/IC 12.1 software (StataCorp LP, College Station, TX, USA).

Results

A total of 2865 patients used atazanavir as their first PI, and of these, 2528 (88%) had sufficient viral load data for the determination of virological failure status, with a median (Q1–Q3) follow-up of 1.76 (0.84–3.15) years. Four hundred and five (16%) patients experienced virological failure, of whom 322 (80%) had one or more valid resistance tests (total of 455 tests).

Patient characteristics relating to the index and control resistance tests are shown in Table 1. Among index patients, atazanavir was typically boosted with ritonavir ($n=251$; 78%) and used in combination with two or more nucleos(t)ide reverse transcriptase inhibitors (NRTIs) ($n=294$; 91%). Common NRTI drugs for those on boosted atazanavir included tenofovir ($n=207$; 82%), emtricitabine ($n=131$; 52%), lamivudine ($n=68$; 27%), abacavir ($n=55$; 22%) and zidovudine ($n=25$; 10%). Those patients on unboosted atazanavir typically had tenofovir ($n=46$; 65%), emtricitabine ($n=26$; 37%), lamivudine ($n=27$; 38%), abacavir ($n=16$; 23%) and zidovudine ($n=14$; 20%) as part of their NRTI backbone. The median (Q1–Q3) time on atazanavir at the time of resistance sampling was 1.28 (0.49–2.73) years and the median (Q1–Q3) time on ART was 2.80 (1.00–5.87) years. Atazanavir was a component of the initial combination ART regimen for 117 (36.3%) patients; for the remainder it was first used in the second-line or subsequent regimen.

Only 6 (1.9%) index patients experiencing virological failure had a major atazanavir-associated mutation, all in isolation: I50L ($n=3$), I84V ($n=2$) and N88S ($n=1$) (Table 2). However, I84V was also observed in 0.32% of control samples, indicating that it cannot necessarily be concluded that it was directly selected by atazanavir. Only 6 of 49 recognized minor atazanavir-associated mutations were significantly associated with atazanavir exposure, although many of these are expected to be selected only as compensatory mutations. The remaining 43 minor atazanavir mutations were either not detected in this dataset (L10C, K20V, E34Q, F53Y, I54L/M/T/A, A71L, G73C/T, V82F and I93M) or were not significantly associated with atazanavir exposure (L10I/F/V, G16E, K20R/M/I/T, L24I, V32I, L33I/F/V, M36L/V, M46L, G48V, I54V, D60E, I62V, I64L/M/V, A71I/T, G73S/A, V82A/I, L90M and I93L). Nine other mutations at six codons (15, 19, 43, 63, 70 and 89) not currently recognized as being associated with atazanavir were significantly more frequent in the index resistance tests compared with the control tests. This included three different substitutions (I, T and V) at codon 89. There was no evidence of a difference between ritonavir-boosted atazanavir and unboosted therapy in terms of individual mutations or in the number of mutations selected (data not shown).

Conclusive evidence that a mutation was directly selected by atazanavir in an individual patient requires demonstration of its absence in a baseline resistance test. However, a baseline test was available in only 137/322 (43%) index patients, limiting the value of this approach. Specifically, none of the patients who were observed to have I15S, K43T, I50L, V82T, I84V, N88S or L89V mutations at virological failure had a baseline resistance test. In almost all patients in whom a baseline resistance test was available, the common M36I and L63P polymorphisms pre-existed prior to exposure to atazanavir.

Discussion

Our findings show that very few patients failing a therapy containing atazanavir are likely to have developed one of the major protease resistance mutations (I50L, I84V and N88S) that confer high-level phenotypic resistance to this drug. However, there was an increased frequency of several other mutations, including I15S, L19T, K43T, L63P/V, K70Q and L89I/T/V, which are not recognized to be associated with atazanavir by the most recent IAS classification. The finding of multiple amino acid substitutions at codons 63 and 89 strengthens the likelihood that mutations at these codons could play a role in atazanavir failure and suggests that atazanavir-induced changes at these sites may have a structural impact on the protease enzyme. Two other mutations, K43T and L89V, have previously been shown to decrease susceptibility to PIs in combination with other mutations.[12] The low frequency of atazanavir-associated resistance mutations in those with virological failure suggests that most virological failures may have been a consequence of suboptimal adherence rather than resistance *per se*. Alternatively, it is possible that determinants of susceptibility to atazanavir lie outside the region of the genome that is examined during routine resistance testing, so could not be detected in this study.[13]

There are two main approaches to examining associations between specific mutations and resistance to individual drugs using clinical data. The first is to examine the effect on clinical response of pre-existing mutations selected by prior exposure to other drugs within that class. In the current context, Vora *et al*.[14] studied 62 patients with prior PI exposure who took boosted atazanavir. They described eight mutations that had an adverse effect on viral load reduction at 3 months, but only two of these (M46I

Table 1. Characteristics of the study population

	Atazanavir-experienced (index) patients $n=322$		PI-naive (control) patients $n=3209$	
	n	%	*n*	%
Gender				
female	86	26.7	920	28.7
male	236	73.3	2289	71.3
Exposure source				
homosexual/bisexual	158	49.1	1598	49.8
heterosexual	132	41.0	1238	38.6
other	20	6.2	129	4.0
unknown	12	3.7	244	7.6
Ethnicity				
white	161	50.0	1621	50.5
black	114	35.4	1022	31.8
other	26	8.1	230	7.2
unknown	21	6.5	336	10.5
Subtype				
A	21	6.5	210	6.5
B	179	55.6	1790	55.8
C	54	16.8	540	16.8
AE	5	1.6	50	1.6
AG	16	5.0	160	5.0
other[a]	16	5.0	149	4.6
unknown	31	9.6	310	9.7
	Median	Q1–Q3	Median	Q1–Q3
Exposure to atazanavir (years)	1.28	0.49–2.73	NA	NA
Time on ART (years)[b]	2.80	1.00–5.87	2.63	0.89–5.31
Age (years)	40.85	35.73–46.01	36.94	31.94–42.91
Year of resistance test	2008	2006–2009	2003	2000–2006
Baseline RNA (log_{10}copies/mL)	4.59	3.75–5.17	4.40	3.51–5.06
Baseline CD4 (cells/mm^3)	289	121–434	303	170–470
RNA at resistance sample (log_{10}copies/mL)	3.36	2.59–4.47	4.20	3.41–4.90
CD4 at resistance sample (cells/mm^3)	315	200–499	290	173–438

NA, not applicable.
[a]Matching not possible for rare CRFs such as CRF11 and CRF13.
[b]In the control group, based on the 2467 (77%) ART-experienced patients.

and I84V) coincided with those identified in our analysis. The second approach, the one adopted in the present paper, is to identify mutations that appear to have emerged under selective drug pressure. Other cohort studies using this approach have tended to focus on highly pre-treated patients, whose patterns of resistance are likely to differ materially from those receiving the drug as the first within that class.[4,15] However, several patients in the IMPACT study, which evaluated atazanavir-containing regimens, were PI naive at enrolment.[3] Although there was a high frequency (7/39) of PI substitutions (including L33I/F and L90M, which we did not observe) in this subgroup, many patients were on NRTI-sparing dual-PI regimens and it is not possible to assess whether the substitutions observed were selected by atazanavir or by the other PI in the regimen.

Our study has several limitations. Despite the large sample of patients who took atazanavir as their first PI, the fact that there were relatively few treatment failures limits the power to detect new resistance mutations. Also, resistance data were not available for all treatment failures and baseline resistance tests were not available for the majority of the subjects. Therefore, some of the mutations detected may have pre-existed as polymorphisms or transmitted mutations. Furthermore, bulk sequencing means that some mutations may have existed as an undetectable minority population at baseline. Indeed, if these pre-existing polymorphisms/mutations reduced the susceptibility to atazanavir and increased the likelihood of virological failure an association would have been induced even if atazanavir did not select for this mutation. Finally, as an exploratory analysis a large number of potential

Table 2. Mutation prevalence by atazanavir experience

		Atazanavir-experienced (index) patients $n=322$		PI-naive (control) patients $n=3209$		
Position	Amino acid	*n*	%	*n*	%	*P* value
Major atazanavir mutations						
50	L	3	0.9	0	0.0	0.001
84	V	2	0.6	10	0.3	0.300
88	S	1	0.3	0	0.0	0.091
Minor atazanavir mutations						
36	I	164	50.9	1436	44.8	0.035
46	I	7	2.2	10	0.3	<0.001
53	L	3	0.9	2	0.1	0.007
71	V	20	6.2	111	3.5	0.019
82	T	2	0.6	0	0.0	0.008
85	V	3	0.9	3	0.1	0.012
Not currently recognized atazanavir mutations						
15	S	2	0.6	2	0.1	0.044
19	T	11	3.4	56	1.8	0.050
43	T	2	0.6	2	0.1	0.045
63	P	149	46.3	1232	38.4	0.007
63	V	11	3.4	45	1.4	0.015
70	Q	2	0.6	2	0.1	0.044
89	I	6	1.9	22	0.7	0.037
89	T	3	0.9	1	0.0	0.003
89	V	2	0.6	1	0.0	0.023

associations were analysed and some of the significant results reported could be false positives.

Further research should continue to monitor drug resistance at virological failure in patients failing first-line atazanavir to assess whether there is an accumulation of further accessory or compensatory mutations in the absence of major resistance mutations. This could result in a re-examination of the concept that atazanavir has a distinct resistance profile with little cross-resistance to other PIs, and that these can therefore be used effectively after failure on atazanavir.[6]

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Coordinating Centre for the UKHDRD

Medical Research Council Clinical Trials Unit (MRC CTU), London (Kate Coughlin, David Dolling, David Dunn, Esther Fearnhill, Lorraine Fradette, Kholoud Porter).

UK CHIC Steering Committee

Jonathan Ainsworth, Jane Anderson, Abdel Babiker, David Chadwick, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard, Richard Gilson, Mark Gompels, Phillip Hay, Teresa Hill, Margaret Johnson, Stephen Kegg, Clifford Leen, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Frank Post, Caroline Sabin (PI), Memory Sachikonye, Achim Schwenk, John Walsh.

Central coordination for UK CHIC

UCL Research Department of Infection and Population Health, Royal Free Campus, London (Teresa Hill, Susie Huntington, Sophie Jose, Andrew Phillips, Caroline Sabin, Alicia Thornton); Medical Research Council Clinical Trials Unit (MRC CTU), London (David Dunn, Adam Glabay).

Participating centres in UK CHIC

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Transparency declarations

None to declare.

Disclaimer

The views in the publication are those of the authors and not necessarily those of the Medical Research Council.

References

1 Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf (26 March 2013, date last accessed).

2 Williams I, Churchill D, Anderson J *et al*. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. *HIV Med* 2012; **13** Suppl 2: 1–85.

3 Zolopa A, Towner W, Butcher D *et al*. Resistance profile after viral rebound on atazanavir-containing therapy: focus on protease inhibitor-naive subjects in the IMPACT Study (BMS AI424–128). *Antivir Ther* 2007; **12** Suppl 1: S86 (Abstract 77).

4 Pellegrin I, Breilh D, Ragnaud JM *et al*. Virological responses to atazanavir-ritonavir-based regimens: resistance-substitutions score and pharmacokinetic parameters (Reyaphar study). *Antivir Ther* 2006; **11**: 421–9.

5 Scherrer AU, Ledergerber B, von Wyl V *et al*. Minor protease inhibitor mutations at baseline do not increase the risk for a virological failure in HIV-1 subtype B infected patients. *PLoS One* 2012; **7**: e37983.

6 Colonno R, Rose R, McLaren C *et al*. Identification of I50L as the signature atazanavir (ATV)-resistance mutation in treatment-naive HIV-1-infected patients receiving ATV-containing regimens. *J Infect Dis* 2004; **189**: 1802–10.

7 Malan DR, Krantz E, David N *et al*. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr* 2008; **47**: 161–7.

8 Cane P, Chrystie I, Dunn D *et al*. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ* 2005; **331**: 1368.

9 The UK Collaborative HIV Cohort Steering Committee. The creation of a large UK-based multicentre cohort of HIV-infected individuals: The UK Collaborative HIV Cohort (UK CHIC) Study. *HIV Med* 2004; **5**: 115–24.

10 Johnson VA, Calvez V, Gunthard HF *et al*. 2011 update of the drug resistance mutations in HIV-1. *Top Antivir Med* 2011; **19**: 156–64.

11 de Oliveira T, Deforche K, Cassol S *et al*. An automated genotyping system for analysis of HIV-1 and other microbial sequences. *Bioinformatics* 2005; **21**: 3797–800.

12 PI Resistance Notes: Stanford University HIV Drug Resistance Database; 2011. http://hivdb.stanford.edu/DR/PIResiNote.html (26 March 2013, date last accessed).

13 Sutherland KA, Mbisa JL, Cane PA *et al*. Contribution of the *gag* gene to variation in susceptibility to protease inhibitors between different strains of HIV-1. *Antivir Ther* 2012; **17** Suppl 1: A17 (Abstract 9).

14 Vora S, Marcelin AG, Gunthard HF *et al*. Clinical validation of atazanavir/ritonavir genotypic resistance score in protease inhibitor-experienced patients. *AIDS* 2006; **20**: 35–40.

15 Bertoli A, Santoro MM, Lorenzini P *et al*. Different patterns of mutations involved in the genotypic resistance score for atazanavir boosted versus atazanavir unboosted in multiply failing patients. *Antivir Ther* 2006; **11** Suppl 1: S99 (Abstract 89).