Clinical outcomes of co-prescription of ranitidine with boosted atazanavir and rilpivirine based ART

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Background

- Although managing drug drug interactions (DDI) is ingrained into daily HIV clinical care, there are few data to support the true clinical implications or outcomes of many of these.
- The non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV) and the protease inhibitor atazanavir (ATV) both require an acid environment in the GI tract for optimal absorption.
- Pharmacokinetics studies demonstrated significant reduction in exposure when co-administered with proton pump inhibitors.
- For patient requiring GI acid suppressive therapy, it is common practice to use the H_2-antagonist ranitidine (RAN) given once daily, 4 to 12 hours after ATV or RPV.
- There are no data describing HIV outcomes in clinical practice for longer term safety of this approach. We report our results from a large prospective London cohort.

Methods

- Single centre, retrospective evaluation of all patients receiving boosted ATV, or RPV (including Eviplera).
- Rates of ATV and RPV discontinuation and viral rebound were calculated stratified by current receipt of RAN.
- It was assumed all RAN was prescribed by the HIV clinic due to the clinical risk, therefore we only considered those patients identified though the local pharmacy dispensing system.
- Patients were followed from the latest of 1/5/2009 or first receipt of ATV/r or RPV until the earliest of 1/5/2015, date of last clinic visit or discontinuation of ATV or RPV.
- For virological analyses, start of follow-up (FU) was delayed until the first date during FU that VL<50c/ml. Subsequent viral rebound was defined as two consecutive VLs>50c/ml.

Results (1)

- Ranitidine was prescribed at some point over follow-up for 7.1% (33/469) and 15.3% (165/1078) of patients on RPV and ATV-based ART, respectively.
- There was a total of 672 and 2603 person years (pyrs) of FU with RPV and ATV respectively, of which 1.9% (13) and 2.9% (76) were spent also receiving RAN.
- The rate of discontinuation from RPV and ATV for those on RAN were higher than those not receiving RAN (table 3).
- Amongst those who discontinued RPV, 100% (5/5) of those with a RAN co-prescription vs 78% (89/114; p=0.58) without RAN had VL<50c/ml. For ATV, these were 72% (21/29) vs 68% (399/585; p=0.63) respectively.
- Of those co-prescribed RAN, 20% (1/5) and 34% (10/29) stopped RPV and ATV due to drug interactions.

Results (2)

Table 1: Baseline demographics of patients receiving rilpivirine- or atazanavir-based ART according to use of ranitidine (RAN)

	% (N) unless stated	Rilpivirine group		Atazanavir group	
		No RAN	RAN	No RAN	RAN
Number patients	N	445	33	985	166
Gender	Male	78 (347)	67 (22)	72 (710)	66 (109)
Age	Median (IQR)	42.9 (37.0, 49.2)	47.2 (40.2, 51.3)	42.8 (36.8, 48.3)	43.5 (38.1, 51.1)
HIV risk	MSM Hetero Other	64 (284) 32 (141) 5 (20)	46 (15) 49 (16) 6 (2)	54 (530) 41 (404) 5 (51)	52 (86) 43 (72) 5 (8)
Ethnicity:	White Black African Other	62 (275) 20 (87) 18 (83)	61 (20) 30 (10) 9 (3)	57 (565) 26 (260) 16 (160)	54 (90) 27 (45) 19 (31)
VL when starting RAN	VL<50c/ml	68 (303)	59 (19)	53 (520)	63 (104)
Baseline CD4	Median (IQR)	588 (34, 787)	647 (359, 840)	510 (336, 700)	525 (322, 707)

Table 2: Rates of virological failure for patients receiving rilpivirine- or atazanavir-based ART according to use of ranitidine (RAN)

ARV	Ranitidine co-prescribed	Baseline ARV status when starting RPV-based ART					
		Switch with VL<50 cps/ml		ART Naïve		Switch with VL>50 cps/ml	
		N events/ pyrs	Rate	N events/ pyrs	Rate	N events/ pyrs	Rate
RPV	Yes	0/6.7	0.00	0/0.9	0.0	0/4.5	0.0
	No	24/423	5.7	6/52.7	11.4	14/96.5	14.5
	P-value		1.00		1.00		1.00
ATV	Yes	5/43.2	11.6	2/1.5	1.3	4/10.6	37.7
	No	139/1281.3	10.9	19/124.2	15.3	110/479.1	23.0
	P-value		0.89		0.004		0.33

Rates given per 100 person-years. aHR= hazard ratio adjusted for ART history, gender, ethnicity, VL and CD4.

Table 3: Rates of discontinuation for patients receiving rilpivirine- or atazanavir-based ART according to use of ranitidine (RAN)

ARV	Ranitidine co-prescribed	ARV discontinuation		
		N events/ pyrs	Rate /100 pyrs (95% CI)	aHR (95% CI)
RPV	Yes	5/12.9	38.0 (12.6-90.5)	-
	No	114/659.2	17.3 (14.1-20.5)	-
	P-value	-	0.077	-
ATV	Yes	29/76.1	38.1 (24.2-52.0)	1.61 (1.10-2.35)
	No	585/2527.3	23.1 (21.3-25.0)	1.00
	P-value	-	0.008	0.0142

Rates given per 100 person-years. aHR= hazard ratio adjusted for ART history, gender, ethnicity, VL and CD4.

Discussion

- Co-prescription of boosted atazanavir or rilpivirine with once daily ranitidine was not associated with increased viral failure, suggesting they are safe to be prescribed together when appropriately separated.
- An increased rate of discontinuation when prescribed ranitidine may be multifactorial.
- As drug drug interaction accounted for only a minority of indications for discontinuations, the need for acid suppressive therapy may indicate other co-morbidities which may influence change of ART.

Limitations

- Small numbers prescribed ranitidine, with limited follow up, in particular for rilpivirine.
- Assumed all ranitidine was prescribed by HIV services.
- Impact of PPI co-prescription not accessed.
- Reason for change of ART extracted local database, rather than formal notes review.

Conclusions

- Co-prescription of boosted atazanavir or rilpivirine with once daily ranitidine was not associated with increased viral failure.
- An increased rate of discontinuation when prescribed ranitidine may be multifactorial.

References

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