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Population and ultra-deep sequencing for tropism determination are correlated with Trofile ES: genotypic re-analysis of the A4001078 maraviroc study

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Background

A4001078 is a study in therapy naive patients of Maraviroc (MVC) plus boosted atazanavir. The Trofile ES (ESTA) was used to determine tropism at Screening. Few re-analyses of genotypic tropism have examined all screened and non-reportable (NR) populations. We aimed to define correlations between methods at screening and evaluate the quantity of X4 using virus in discordant results using ultra-deep sequencing (UDS).

Methods

Population and UDS methods were employed on 178 of 220 screened subjects and 121 enrolled subjects. Correlation between methods was explored and the quantity of X4-using virus in both discordant and concordant samples was measured using UDS.

Results

ESTA defined 123 (69%) as R5, 39 (22%) as Dual or Mixed tropism (D/M) and 16 (9%) as NR. Population sequencing (single amplification) defined 146 (82%) as R5, 26 as X4, and 6 tests were non reportable [Either failure to get a PCR product (no result for both, population sequencing and UDS) or non-evaluable Sanger traces]. Correlation between population and UDS for R5 use was 95%. Of the patients screened as R5 by population sequencing, UDS showed a median of 0% X4 with only 3 of 114 results being over 2% X4 use, suggesting this method is suitable for selecting individuals for CCR5 antagonist therapy. All Trofile NR results were reportable by population sequencing and showed tropism results consistent with the overall population.

Trofile ES Result	Population sequencing with a 5.75 FPR (g2p) UDS Median % X4 use (IQR%)			UDS result with 2% cut off (at g2p FPR of 3.5) Median % (IQR%)		
	R5	CXCR4 using	NR	R5	CXCR4 Using	NR
R5 = 123	114 0 (0)	5 47.5 (29)	4 0 (0)	111 0 (0)	7 47.5 (64.8)	5 NA
D/M = 39	19 0.11 (0.4)	18 43.3 (59.9)	2 0.54 (0)	14 0 (0.3)	22 39.4 (57.7)	3 NA
NR = 16	13 0 (0.04)	3 73.1 (97.7)	0	13 0 (0.1)	2 86.4 (26.7)	1 NA

Figure 1 Correlation between methods and quantity of X4 use by UDS in concordant and discordant results and quantity of X4 using virus by UDS.

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Conclusions

Population sequencing appropriately identified patients with <2% CXCR4 using virus and who would be suitable for CCR5 antagonist therapy.

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