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PREVALENCE OF LOW ABUNDANT DRUG-RESISTANT VARIANTS BY ULTRA-DEEP SEQUENCING IN CHRONICALLY HIV-INFECTED ANTIRETROVIRAL (ARV)-NAÏVE PATIENTS AND THE IMPACT ON VIROLOGICAL OUTCOMES

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BB Simen¹, K Huppler Hullsiek², RM Novak³, RD MacArthur⁴, JD Baxter⁵, C Huang¹, C Lubeski¹, GS Trenchalk¹, MS Braverman¹, B Desany¹, JF Simons¹, JM Rothberg¹, M Egholm¹ and MJ Kozal⁶

¹454 Life Sciences, Branford, CT, USA; ²University of Minnesota, Minneapolis, MN, USA; ³University of Illinois, Chicago, IL, USA; ⁴Wayne State University, Detroit, MI, USA; ⁵Cooper University Hospital/UMDNJ-Robert Wood Johnson Medical School, Camden, NJ, USA; ⁶Yale University School of Medicine, New Haven, CT, USA

BACKGROUND: Low abundant drug-resistant HIV variants can rapidly grow under drug-selection pressure and lead to treatment failure. Although point mutation assays can identify selected mutations, there are >80 mutations associated with HIV drug resistance. New methods are needed to detect all the possible resistance mutations that can be present in the numerous different viral variants in a clinical sample.

OBJECTIVES: For chronically infected, ARV-naïve FIRST study participants, determine the prevalence of low abundance drug-resistant variants using ultra-deep sequencing, compare the prevalence between ultra-deep and standard sequencing, and determine the impact of minor-resistant variants on virological responses.

METHODS: The FIRST study randomized ARV-naïve persons to (1) PI+NRTIs, (2) NNRTI+NRTIs, or (3) PI+NNRTI+NRTI(s). A subset ($n=195$) had baseline drug resistance determined by both standard genotyping (TRUGENETM) and ultra-deep sequencing (minor variant detection at 1–3% levels). IAS-USA mutations were evaluated for by both methods; all Stanford HIV drug resistance database mutations (HDRM) were also evaluated for with ultra-deep sequencing. The standard and ultradeep sequencing methods were compared with McNemar's test for dependent proportions. Proportional hazards models were used to compare those with and without mutations for virological failure (VF; HIV RNA >1,000 copies/ml).

RESULTS: At least one IAS-USA mutation was detected at baseline by standard and ultra-deep sequencing for 12.8% and 20.0% of participants, respectively ($P=0.007$). Stanford-HDRM were detected by ultra-deep sequencing in 30.8% of participants. Ultra-deep sequencing identified IAS-defined NNRTI, NRTI, and PI mutations in 8.2%, 11.3%, and 3.5% of participants, respectively; Stanford-HDRM NNRTI, NRTI, and PI mutations were detected in 16.4%, 15.4%, and 4.1%. Among those in the NNRTI+NRTIs arm of FIRST, all participants with a NNRTI mutation identified experienced VF, and the risk for VF was significantly higher for those with NNRTI mutation(s) at baseline by ultra-deep sequencing compared to those without a NNRTI mutation (HR 2.8, 95% CI 1.0–7.9, $P=0.05$ for IAS-mutations; HR 2.3, 95% CI 1.1–5.0, $P=0.03$ for Stanford-HDRM).

CONCLUSIONS: Ultra-deep sequencing identified a significantly larger proportion of chronically infected ARV-naïve patients harbouring drug-resistant variants than standard resistance genotyping. For those who initiated ART within the NNRTI arm of FIRST, the risk of virological failure was significantly greater for participants with low abundant NNRTI-resistant variants identified by ultra-deep sequencing than for those without NNRTI resistance identified.

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134

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