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BULK SEQUENCE-DETECTABLE RESISTANCE MUTATIONS IN PERIPHERAL RNA FOLLOWING SINGLE-DOSE NEVIRAPINE ARE ASSOCIATED WITH POORER TREATMENT RESPONSES BUT DO NOT ADEQUATELY EXPLAIN TREATMENT FAILURE

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BACKGROUND: Sensitive drug resistance testing has revealed that drug resistance emerges in the majority of women exposed to single-dose nevirapine (sdNVP), raising concern for future treatment responses. We examined sdNVP-associated mutations by bulk sequencing and sensitive real-time PCR to determine variant levels and patterns associated with poor treatment response.

METHODS: Viral RNA from 162 sdNVP-exposed and 265 sdNVP-unexposed Zambian women were baseline-tested for nevirapine-associated mutations prior to beginning nevirapine/efavirenz-based antiretroviral therapy. Bulk sequencing evaluated reverse transcriptase codons 1–251 and real-time PCR screened only sdNVP-exposed women for K103N, V106M, Y181C and G190A. Presence of baseline majority and/or minority mutations and time since sdNVP exposure were assessed against treatment failure (VL>400 copies/ml) at 24 or 48 weeks.

RESULTS: Bulk sequencing detected 15 mutations in 13 (5%) sdNVP-unexposed women, including four A98G, four V179D, two K101E, two K103N, and one each of V106M, V108I and G190A. Twenty-eight (17.5%) sdNVP-exposed women had sequence-detectable mutations: 20 at <6 months, one between 7 and 12 months, and seven >12 months after exposure (X^2 trend $P<0.0001$). Sensitive testing

detected variants of the four mutations assayed in 53/162 (33%) sdNVP-exposed women. SdNVP-exposed women with no detectable or only minority baseline mutations responded similarly to therapy (27% versus 18% failure; $P=0.3$). Among women with a sequence-detectable mutation at baseline, only 1/13 (0.8%) sdNVP-unexposed women experienced failure compared with 13/24 (54%) exposed women ($P=0.01$). For this latter group, the association with failure was strengthened by the subsets who also had minority mutations (8/13 failed) and those with A98G (3/4 failed). The four sdNVP-unexposed women with A98G did not experience failure. SdNVP-exposed women without detectable mutations were 1.8× more likely to fail than sdNVP-unexposed women (27% versus 15%; $P=0.01$). Regardless of detectable resistance, virological failure was greater (40%) when treatment was initiated <6 months after sdNVP (27% 7–12 months and 22% >12 months; X^2 trend $P=0.03$).

CONCLUSIONS: Although minority mutations when present with sequence-detectable mutations strengthened the association with failure, they alone did not predict failure. Even in the absence of detectable resistance, sdNVP-exposed women, when compared with unexposed, experienced significant virological failure close to the time of sdNVP exposure possibly suggesting transient resistance sanctuaries not readily detectable in peripheral viruses.

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