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LOW FREQUENCY K103N MUTATIONS ARE STRONGLY ASSOCIATED WITH INADEQUATE VIROLOGICAL RESPONSES TO NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR BASED THERAPY

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BACKGROUND: Single-dose nevirapine (sdNVP) used for prevention of mother-to-child HIV transmission is associated with the selection of viral resistance mutations, notably the K103N mutation of reverse transcriptase. In the absence of drug pressure, these variants are shown to fade over time to low levels. Recently developed methods such as the allele-specific PCR (AS-PCR) are capable of detecting lower frequencies of mutant variants than conventional genotyping assays. However, the clinical relevance of these minority variants on treatment outcomes has not been fully established.

METHODS: An observational epidemiological study was conducted in Johannesburg, South Africa, in which initial and sustained virological response to first-line therapy (stavudine+lamivudine+nevirapine/efavirenz) was compared between 94 HIV-infected women previously exposed to sdNVP 18–36 months earlier and 60 previously pregnant women who were unexposed. Pretreatment samples were tested for K103N mutations using an allele-specific real-time PCR and population sequencing was performed on samples from patients with inadequate virological responses.

RESULTS: K103N mutations were detected by AS-PCR among 10.6% sdNVP-exposed women and 15% unexposed reportedly drug-naïve women prior to therapy. Of those with baseline resistance, 57.8% had a subsequent inadequate virological response, defined as either not achieving a viral load <50 copies/ml or not sustaining viral suppression to 78 weeks. However, out of the 30 women in both groups with

inadequate virological response, only 36.7% had K103N detected by AS-PCR pretreatment suggesting that other minority mutant populations need to be analyzed. Population sequencing of the earliest failing sample revealed a different profile of mutations between the sdNVP-exposed and -unexposed women: K103N was more common among the exposed (9/18, 50%) than the unexposed group (3/12, 25%) whereas M184V/I was more common among the unexposed (9/12, 75%) than the exposed group (6/18, 33%). However, in both groups the majority had at least one non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutation; 13/18 (72%) among sdNVP-exposed and 10/12 (83%) among unexposed women in their failing sample.

DISCUSSION: Approximately 10% of women participating in this study had K103N mutations detected pretreatment, irrespective of their reported prior exposure to sd-NVP for prevention of mother-to-child transmission. These K103N mutations were shown to be strongly associated with inadequate virological responses to NNRTI-based therapy.

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