Abstract

BACKGROUND:

Transmitted drug resistance (TDR) is increasing in some areas of Africa. Detection of TDR may predict virologic failure of first-line nonnucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART). We evaluated the utility of a relatively inexpensive oligonucleotide ligation assay (OLA) to detect clinically relevant TDR at the time of ART initiation.

METHODS:

Pre-ART plasmas from ART-naive Kenyans initiating an NNRTI-based fixed-dose combination ART in a randomized adherence trial conducted in 2006 were retrospectively analyzed by OLA for mutations conferring resistance to NNRTI (K103N, Y181C, and G190A) and lamivudine (M184V). Post-ART plasmas were analyzed for virologic failure (Ó1000 copies/mL) at 6-month intervals over 18-month follow-up. Pre-ART plasmas of those with virologic failure were evaluated for drug resistance by consensus and 454-pyrosequencing.

RESULTS:

Among 386 participants, TDR was detected by OLA in 3.89% (95% confidence interval: 2.19 to 6.33) and was associated with a 10-fold higher rate of virologic failure (hazard ratio: 10.39; 95% confidence interval: 3.23 to 32.41; $P < 0.001$) compared with those without TDR. OLA detected 24 TDR mutations (K103N: n = 13; Y181C: n = 5; G190A: n = 3; M184V: n = 3) in 15 subjects (NNRTI: n = 15; 3TC: n = 3). Among 51 participants who developed virologic failure, consensus sequencing did not detect additional TDR mutations conferring high-level resistance, and pyrosequencing only detected additional mutations at frequencies <2%. Mutant frequencies <2% at ART initiation were significantly less likely to be found at the time of virologic failure compared with frequencies Ó2% (22% vs. 63%; $P < 0.001$).

CONCLUSIONS:

Detection of TDR by a point mutation assay may prevent the use of suboptimal ART.