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Cross-sectional assessment of virological failure, drug resistance and third-line regimen requirements among patients receiving second-line ART in 3 large HIV programmes in Kenya, Malawi and Mozambique

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Introduction: With access to viral load (VL) monitoring, the number of patients receiving second-line antiretroviral treatment (ART) is increasing in resource-limited countries. We assessed virological response and second-line drug resistance in three large HIV-programmes to inform regimen-requirements, to evaluate patient outcomes and support forecasting of effective third-line drugs.
Methods: Between November 2014 and December 2015, patients aged ≥5 years receiving a standard second-line regimen for ≥6 months were recruited in three HIV outpatient-clinics supported by Médecins Sans Frontières in Kenya, Malawi and Mozambique. VL was quantified and resistance-genotyping performed if VL ≥500 HIV RNA copies/ml (virological failure). Sequences were interpreted with Stanford and ANRS algorithms. Virological failures are assessed 6 and 12 months after counselling or regimen change.
Results: A total of 824 patients were included (median age 41 years, 45.4% males). In Kenya, among 355 participants (26.9 month median duration of second-line; 71.6% 3TC-TDF-LPV/r), 18.3% (65/355) had VL ≥500 copies/ml, 16.9% ≥1000 copies/ml. Among those aged ≥19 years, 31.2% (20/64) had ≥500 copies/ml. Overall 24.6% (16/65) had major PI-resistance, 72.3% major NRTI-resistance, 80% major NNRTI-resistance, and 9.2% major etravirine-resistance (Stanford). Nineteen patients (29.2%) required replacement of ineffective NRTIs, 21 (32.3%) needed to start a third line regimen (change of PI-component), with three children requiring paediatric formulations. Six months after regimen change 77.8% (14/18) had VL <20 copies/ml. In Malawi: among 242 patients (36.3 month median duration of second-line; 81.4% 3TC-TDF-ATV/r), 16.5% had VL ≤500 copies/ml, 13.2% ≤1000. Among those aged ≤19 years, 29.4% (10/34) had VL ≤500. Sequencing (37/40) detected 2.9% major PI-resistance, 78.4% major NRTI-resistance, 83.8% major NNRTI-resistance, 18.9% major etravirine-resistance. Seven patients required switch to a third-line regimen, 12 required NRTI-replacement. Complete resistance and regimen data will be available from all sites, including Mozambique (227 patients, 91.2% TDF-3TC-LPV/r).
Conclusions: These findings indicate good virological suppression in patients receiving second-line ART. Failure rates were notably higher among children and adolescents, highlighting the need for enhanced monitoring. Resistance data were essential to inform optimal regimen choice. Preliminary results indicate good short-term outcomes of patients who needed ART change. Increased access to resistance genotyping and affordable salvage ARVs, including paediatric formulations, are needed.

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Effect of PI resistance mutations on viral load in patients on PI monotherapy

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Introduction: Protease inhibitor (PI) resistance mutations are uncommon in patients failing boosted-PI (bPI) containing regimens; longitudinal data assessing impact of PI resistance on outcomes are sparse.
Methods: We assessed the development of PI-resistance mutations over time in patients failing first-line NNRTI-based regimens and randomized within the EARNEST trial to bPI-monotherapy (standardized to lopinavir/ritonavir bd, with 12-week raltegravir induction to induce rapid VL suppression). VLs and resistance tests were performed blinded. Resistance testing was done retrospectively in one laboratory on all stored samples (12–16 weekly) between first confirmed virological failure (VL >1000 copies/ml) and switch to combination therapy.
Results: A total of 405 patients started bPI-monotherapy and had ≥1 follow-up VL sample. Median treatment duration was 108 (IQR: 98–124) weeks until switch to combination therapy following an interim review. One hundred forty-eight (37%) developed virological failure on bPI-monotherapy. Median VL at bPI-monotherapy failure was 3681 c/ml, subsequently increasing by 0.48$\log_{10}$ c/ml per year (95% CI: 0.31–0.65). 28(26%) of the 106 with genotypes at bPI-monotherapy failure had major/minor PI mutations, increasing to five (62%) of the eight with genotypes 96 weeks after failure. The most common mutations were V82A (39%), I54V (39%) and M46I (32%). Rate of emergence of new mutations peaked at 37 weeks after failure (1.81 mutations/year; 95% CI: 1.31–2.51;