Abstract Access to antiretroviral therapy (ART) is increasing in resource-limited settings (RLS) and can successfully reduce HIV-related morbidity and mortality. However, virologic failure and development of viral drug resistance can result in reduced treatment options and disease progression. Additionally, transmission of resistant virus, and particularly multi-drug resistance, could become a public health concern. This study evaluated treatment success and development of ART drug resistance after short-term treatment among patients attending the Comprehensive HIV Care Centre (CCC) of Coast Province General Hospital, Mombasa, Kenva. One hundred and fifty HIV-infected individuals receiving ART were consecutively recruited to participate in the study. After determination of plasma viral load, patients with detectable viral load levels were subjected to genotypic drug resistance testing. At the time of sampling, 132 of the 150 participants were on ART for more than 6 months (median 21 months, IQR = 12–26). An efficient viral load reduction to below 50 copies/ml was observed in 113 (85.6%) of them. Of the 19 patients with a detectable viral load, sequencing of the protease (PR) and reverse transcriptase (RT) gene was successful in 16. Eleven (11) of these 16 patients were infected with a subtype A1 virus. Major PR mutations were absent, but mutations associated with drug resistance in RT were detected in 14 of the 16 patients (87.5%). High-level resistance against at least 2 drugs of the ART regimen was observed in 9/14 (64.3%). The 3TC mutation M184V and the NNRTI mutation K103N were most frequent but also the multidrug resistance Q151M and the broad NRTI cross-resistance K65R were observed. The results of this study revealed a high rate of treatment success after short term ART in patients treated at a public provincial hospital in a RLS. Nevertheless, the observed high risk of accumulation of resistance mutations among patients failing treatment and the selection of multi-drug resistance mutations in some, remains of great concern for future treatment options and potential transmission to partners.