**Background**: We reported very low rates (4%) of virologic failure (VF) for patients after 6 months of first-line ART at two urban clinics in Durban, South Africa. However, rates of VF are higher in peri-urban and rural sites in South Africa (20-40%). We therefore sought to ascertain the individual-level factors associated with VF in this urban setting and develop an effective, feasible adherence measure in order to identify patients at risk for VF earlier in the course of ART.

**Methods**: A case-control study was conducted at McCord Hospital in Durban, South Africa. Cases were defined as patients with VF (viral load, VL > 1000 copies/mL) after > 5 months of first line ART and controls (2:1) were defined as patients with VL < 1000 copies/mL after > 5 months of first-line ART. Adherence was measured as one minus the ratio of pill count over total number of pills dispensed during the study period. A semi-structured questionnaire including validated psychosocial and symptom measures was administered to all participants and additional data were collected from the medical record. Covariates were compared between cases and controls. A final multivariate (MV) logistic regression model of VF included factors found to be associated with VF (p<0.05) as well as age, gender, and duration on ART regimen.

**Results**: A total of 158 cases and 300 controls were enrolled from October 2010 to June 2012. Median age was 38.4 years (mean±sd=39.6±9.0), 64.6% were women, median CD4 cell count 254 cells/uL and median VL 95,221 copies/mL for cases. In unadjusted analyses, adherence was significantly lower among cases than controls (p=0.0015). Adherence persisted as a significant predictor even after adjusting for age, gender, number of opportunistic infections, duration of ART, employment status, presence of support network, contraceptive use, and levels of fatigue, depression, and nervousness. All covariates were significant in unadjusted analyses but only age, gender, duration of ART, fatigue, and support network remained significant in the MV model. Nervousness was of borderline significance (p=0.086) in the MV model.

**Conclusions**: Pill counts combined with pharmacy refill data can provide a useful surrogate for VF serving as a potential ‘Early Warning Indicator’ in advance of routine VL monitoring. Adherence interventions may be targeted earlier for patients using this measure. Younger age, male gender, poor social support and stress-related symptoms are associated with VF independent of adherence metrics.