**Background**: We reported very low rates (4%) of virological failure (VF) for patients after 6 months of first-line ART at two clinics in Durban, South Africa. However, rates of VF are higher in peri-urban and rural sites in South Africa (20-40%). We sought to ascertain the individual-level factors associated with VF 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 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, 64.6% were women, 98.7% black, CD4 254 cells/µL and 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, length on ART, employment status (income or not), fatigue, depression, nervousness, presence of support network, and contraceptive use. All covariates were significant in unadjusted analyses but only age, gender, duration on ART, fatigue, and support network remained significant in the MV model. Nervousness was mildly significant (p=0.086) in the MV model.

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