**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 in order to identify patients at risk for VF earlier in the course of ART.

**Methods**: This was a planned midpoint analysis of an ongoing case control study of VF conducted at McCord hospital in Durban. Cases were defined as patients with VF (viral load, VL > 1000 copies/mL) after > 6 months of first line ART and controls (2:1) were defined as patients with VL < 1000 copies/mL after > 6 months of first-line ART. Pharmacy refill and pill counts were used as adherence measures. 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 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/uL and VL 95,221 copies/mL for cases. In unadjusted analyses, the estimate for par score (adherence rates=100-pill\_count/dispense\*100) is -0.0518±0.0163 (p=0.0015) with the odds ratio=0.95[0.92-0.98]. The par score persisted significantly even after adjusting for age, gender, number of opportunistic infections, ART. Age, gender, ART, at-home support network, fatigue from the symptoms scale remained significant in the MV model. Additional variables of interest including employment status (have income or not), depression, nervousness, and contraceptive use, were each associated with VF in unadjusted analyses but could not be included in the final model due to potential collinearity.

**Conclusions**: Pill counts combined with pharmacy refill data can provide a useful surrogate for VF serving as Early Warning Indicators in advance of routine VL monitoring. Adherence interventions may be targeted earlier for patients using these measures. Younger age and stress-related symptoms are associated with VF independent of adherence metrics. Additional risk factors including poor socioeconomic conditions, support and depression will need further exploration.