Oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) has been evaluated as pre-exposure prophylaxis (PrEP). We describe the accuracy of self-reported adherence to FTC/TDF and pill counts when compared to drug concentrations in the FEM-PrEP trial. Using drug concentrations of plasma tenofovir (TFV) and intracellular tenofovir diphosphate (TFVdp) among a random sub-sample of 150 participants assigned to FTC/TDF, we estimated the positive predictive value (PPV) of four adherence measures. We also assessed factors associated with misreporting of adherence using multiple drug-concentration thresholds and explored pill use and misreporting using semi-structured interviews (SSIs). Reporting use of ≥1 pill in the previous 7 days had the highest PPV, while pill-count data consistent with missing ≤1 day had the lowest PPV. However, all four measures demonstrated poor PPV. Reported use of oral contraceptives (OR 2.26; \( p = 0.014 \)) and weeks of time in the study (OR 1.02; \( p < 0.001 \)) were significantly associated with misreporting adherence. Although most SSI participants said they did not misreport adherence, participant-dependent adherence measures were clearly unreliable in the FEM-PrEP trial. Pharmacokinetic monitoring remains the measure of choice until more reliable participant-dependent measures are developed.