In HIV-1 infection, plasma viral load (VL) has dual implications for pathogenesis and public health. Based on well-known patterns of HIV-1 evolution and immune escape, we hypothesized that VL is an evolving quantitative trait that depends heavily on duration of infection (DOI), demographic features, human leukocyte antigen (HLA) genotypes and viral characteristics. Prospective data from 421 African seroconverters with at least four eligible visits did show relatively steady VL beyond 3 months of untreated infection, but host and viral factors independently associated with cross-sectional and longitudinal VL often varied by analytical approaches and sliding time windows. Specifically, the effects of age, HLA-B(53) and infecting HIV-1 subtypes (A1, C and others) on VL were either sporadic or highly sensitive to time windows. These observations were strengthened by the addition of 111 seroconverters with 2-3 eligible VL results, suggesting that DOI should be a critical parameter in epidemiological and clinical studies.