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Sensitive population profiling and genome assembly of HIV and Flaviviruses using ultra-deep sequencing technologies

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Viral diseases such as HIV/AIDS and Dengue have an enormous impact on human health worldwide. Despite this, application of new sequencing technologies to viral genomics has lagged. We are using genome sequence data to study how populations of single stranded RNA viruses, including HIV, Dengue, West Nile and Hepatitis C, evolve within infected individuals in response to host immune, therapeutic and vaccine pressures. To support this, we have developed high-throughput sequencing, assembly and population profiling pipelines based on 454 and Illumina technology that are tuned to the specific needs of viral sequencing. These strategies can capture full genome sequences and can profile sequence diversity at each residue in the genome with unprecedented sensitivity. Our analytical pipeline for 454 and Illumina data (i) generates complete genome assemblies from short sequencing reads derived from populations with high rates of variation; and (ii) detects and quantifies variants in these populations with high sensitivity, while differentiating true variants from process errors.

Initial results with our viral sequencing and analysis pipeline are extremely promising. We detected rare variants to below 1% frequency, revolutionizing our ability to accurately assess the earliest events in viral evolution. We have demonstrated effective assessment of genome-wide diversity during acute HIV infection, enabling rapid, affordable, and highly sensitive identification of the earliest cellular immune responses to HIV. This has allowed us to detect earlier evolutionary events, demonstrating, for example, that HIV cytotoxic T-lymphocyte (CTL) escape can occur much faster than previously known. In addition, we have shown that the extent of intra-host diversity in Flaviviruses such as DENV and WNV is different between these closely related viruses with the latter exhibiting greater genetic diversity. The results presented here demonstrate the power of scalable, next generation sequencing-based methodologies as a genome-wide and unbiased global approach to profiling genomic diversity in intra-host populations of single stranded RNA viruses.

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