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Simulation of Pooled Nucleic Acid Testing to Identify Antiretroviral Treatment Failure During HIV Infection in Seoul, South Korea

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Monitoring HIV RNA levels (viral loads) every 3–6 months is recommended in patients receiving antiretroviral therapy (ART) because HIV replication is the most important indicator of treatment response. In high-resource settings, regular viral load monitoring is a standard of care[1] but not in resource-constrained settings.[2] Currently, the number of patients receiving ART is growing in resource-limited regions and so are the needs for monitoring for treatment failure and development of drug resistance. Because of the high cost of viral load testing, virological monitoring has been substituted by clinical and immunologic monitoring in those regions, but the effectiveness is poor.[2,3] There are various efforts to identify less costly but still accurate method for monitoring treatment response in resource-limited setting, and a pooling strategy has been proposed.[4-7]

In theory, pooled testing can decrease the cost of monitoring by reducing the number of assays needed to screen a population receiving ART,[4-7] similar to the pooled nucleic acid testing (pooled NAT) used to screen for acute HIV infection among individuals presenting for HIV testing or blood donation.[8-10] The usefulness of pooled NAT to detect ART failure could be affected by several factors, including rate of virologic failure, assay platform, level of detection, inherent error of assay type, laboratory space to avoid contamination during processing, and personnel availability and expertise.[5] Therefore, studies about use of pooling NAT for monitoring treatment failure in various circumstances are needed. Three pooling approaches have been evaluated in previous studies, including minipools, minipool + algorithm, and matrix + algorithm.[4] Each of these approaches demonstrated a reduction in the number of assays that need to screen a population receiving ART with minimal decrease in sensitivity to detect ART failure, that is, “relative efficiency.”[4,5] However, relative efficiency varied by each approach, and the addition of an algorithm for determining the deconvolution of pools greatly enhanced the relative efficiency. Specifically, the minipool approach showed the lowest efficiency, and the matrix approach with 8 or 10 pool size was the most efficient. The minipool + algorithm approach showed intermediated efficiency, and among them, the one with pool size of 5 samples (5 minipool + algorithm) showed highest

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efficiency. It is also the strategy with the least likely technical errors.[4] Based on previous studies, the matrix + algorithm approach could potentially save more than the minipool + algorithm, but the matrix platform has been demonstrated to be more technically demanding with greater chance for contamination.[6] Moreover, the matrix approach requires more samples before testing can be performed, which could lead to longer turnaround time and is likely not feasible at our institution. Therefore, we pursued evaluation of the minipool + algorithm approach.

Based on these previously published data and liberally assuming that the accuracy of minipool + algorithm strategy would be 100%, we calculated at what rate of virologic failure would the minipool + algorithm strategy demonstrate improvement over testing samples individually. Specifically, the relative efficiency of the minipool + algorithm would be a point from "1 − ((1/N) + NR)" to "1 − ((1/N) + R)" [R = rate of virologic failure among the individual samples, N = number of samples per one pooling test (pool size)]. Accordingly, the minipool + algorithm approach would be more efficient than individual testing when the rate of virologic failure (R) is lower than $((1/N) - (1/N^2))$. As an example, 5 minipool + algorithm approach could be useful when the virologic failure rate is <16%.

We then performed simulations of a 5 minipool + algorithm strategy using individual viral load data collected from patients receiving ART for >6 months between January 2009 and December 2010 at our urban Korean hospital. The viral load assay used (Roche COBAS AmpliPrep/COBAS TaqMan) has a lower level of detection of 20 HIV RNA copies/mL, and the cost per assay is 152,970 won (USD $136). Exceeding 200 copies/mL of HIV RNA was defined as virologic failure according to recent HIV care guidelines.[1] In this demonstration evaluation, both actual individual test and simulated pooled assay were assumed to have no measurement error; however, viral load values were evaluated based on a gamma distribution of categories.

During the 24-month period, 1577 viral loads were performed for 351 HIV patients who were receiving ART for >6 months. The overall virologic failure rate was 9.7% when the cutoff value of HIV-RNA level was 200 copies/mL, while the distribution of viral loads (copies/mL) was <20 (85.7%), 20–200 (4.7%), 200–1500 (3.5%), 1500–10,000 (2.2%), 10^4–10^6(3.6%), and >10^6(0.4%). Based on these data, we selected the 5 minipool + algorithm for the following simulation.

We arranged the viral load sample data in chronological order assuming that testing would be performed in order of prescription. Based on the minipool + 5 algorithm, 730 tests were needed in simulation to screen all samples for ART failure, representing 847 tests saved and a relative efficiency of 0.54. Converting the tests to cost, a total of USD $115,192 would have been saved. Since the threshold of viral load for defining treatment failure in our study was different from the previous study, and the threshold varied by each previous study,[4-7] we also investigated the threshold of 1500 copies/mL and found that at 1500 copies/mL, the virologic failure rate would be reduced from 9.7% to 6.2%, and the subsequent relative efficiency would be 0.62.

In conclusion, the pooled NAT strategy with 5 minipool + algorithm seems to be a very promising approach to effectively monitor patients receiving ART and save resources in South Korea. However, this study was conducted retrospectively and in simulation, so we could not analyze the turnaround time or accuracy, which could impact the usefulness of this approach; therefore, a prospectively designed study should be conducted.

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