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Cost Ramifications of Increased Reporting of Detectable Plasma HIV-1 RNA Levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Version 1.0 Viral Load Test

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To the Editors:

HIV treatment guidelines state the goal of antiretroviral therapy (ART) is virologic suppression [plasma HIV viral load (VL) below 50 copies/mL] for patients on initial and subsequent regimens.[1] Assays measuring HIV-1 RNA VL levels have been a cornerstone in the evaluation of successful ART since 1996.[2,3] Providers depend on serial VL measurements to gauge treatment success and to provide early evidence of failing ART. Over the past decade, a series of assays, each with increased ability to detect progressively lower VL levels, have been released.[4] In 2008, Roche Diagnostics released the COBAS Ampliprep/COBAS TaqMan HIV-1, v.1.0 assay (TaqMan). Due to ease of performance (more automated, requiring less manual intervention), a wider linear dynamic range (both lower and higher limits of detection: 48 to 1×10^7 copies/mL) and similar sensitivity and specificity to the previous VL

assay [Roche COBAS HIV-1 Ampliprep Amplicor Monitor Test, v.1.5 (Amplicor)], the University of Alabama at Birmingham (UAB) clinical hospital laboratory transitioned to TaqMan as its primary VL assay on June 9, 2008. [5,6]

Following the transition to TaqMan, multiple HIV care providers at the UAB 1917 HIV/AIDS Clinic (1917 Clinic) reported an increase in the number of patients with HIV-1 VL>50 copies/mL who had previous long-term virologic suppression (VL<50 copies/mL). These anecdotes were supported by quarterly clinic quality control data as the year prior to TaqMan use, 60-63% of patients on ART achieved VL suppression, while after its introduction this percentage steadily decreased each quarter falling to a low of 49% (January-March 2009). In vitro evidence and reports from other sites have questioned the clinical implications of employing the TaqMan assay at the lower end of the dynamic range due to increased reports of detectable VL levels and viral load “blips” in previously well-controlled individuals. [7-10] In order to explore the impact of the change to the TaqMan assay on our clinic population, we sought to quantify the number of elevated VL readings in previously well-controlled patients during the first year of TaqMan use; and determine the costs associated with the increased frequency of these reported VL elevations.

The UAB 1917 HIV/AIDS Clinic Cohort is an IRB approved protocol that has been previously described.[11] We conducted a retrospective study nested in the UAB 1917 Clinic Cohort among virologically suppressed patients on ART, at the time of implementation of the TaqMan assay.

Patients meeting the following criteria were included: 1) Initiated ART prior to 9/10/07; (2) ≥ 1 VL measurement in the defined pre-TaqMan (9/10/07-6/8/08) and TaqMan (6/9/08-4/10/09) observation periods; (3) All reported VL values in the pre-TaqMan period <50 copies/mL and no ART changes, indicating well controlled HIV. Patients meeting criteria were classified as having undetectable (all VL<50 copies/mL) and detectable (≥1 VL>50 copies/mL) VL following implementation of the TaqMan assay.

Bivariate analyses (chi-square, T-test) of patient characteristics, including age, sex, race, insurance status, place of residence, number of visits, HIV risk factor, and number of CD4 and VL measures in each time period were performed. The differences in frequency of VL and CD4 test ordering before and after TaqMan implementation were established. The total materials cost for the additional laboratory testing (VL, CD4, resistance tests) was calculated. The results of repeated VL tests in the TaqMan era detectable VL population are described. The number and outcomes of resistance tests ordered among patients with previously controlled VL after the transition to the TaqMan assay were quantified. All statistical analyses were performed using SAS software version 9.1.3.

Among 434 patients meeting inclusion criteria, 236 (54%) maintained VL suppression following implementation of the TaqMan assay, whereas 198 (46%) had detectable viremia (>50 copies/mL). Male gender was more common in the TaqMan detectable group ($p<0.03$), but there were no other significant differences between groups across study variables. In the pre-TaqMan period, a mean 2.07±1.01 VL measures were ordered per patient. Patients with detectable VL measures following TaqMan implementation underwent more VL testing than those that remained undetectable (2.34±0.96 vs. 2.10±1.09 respectively, $p<0.01$). Compared to the pre-TaqMan era, the mean number of VL tests performed increased by 0.40±1.15 per patient in those with detectable viremia versus a decrease of 0.08±1.18 among those with sustained VL suppression ($p<0.01$). A statistically significant change ($p<0.01$) in CD4 test ordering was also seen in the TaqMan detectable group following TaqMan implementation (0.31±1.09 vs. -0.05±1.26 in the sustained VL suppression group).

By multiplying the differences in frequency of test ordering before and after implementation of the TaqMan assay by the number of detectable patients (n=198) following assay release, we estimated an additional 79 VL and 61 CD4 tests were ordered. The estimated cost of these additional tests was US $22,358.00 ($172.00 per VL test, $136.00 per CD4 test, $6.00 per venipuncture/collection fee—1917 Clinic, April 2009).

The number and range of VL values observed among the 198 patients with newly detectable viremia following TaqMan implementation were: 124 (63%) 51-400, 36 (18%) 401-1000, 30 (15%) 1001-5000 and 8 (4%) >5000 copies/mL. Of these, 149 patients (75%) had a subsequent TaqMan VL measure within the study period and the majority of these VL tests were undetectable (n=90, 60%). Among those with detectable viremia, there were six people for whom seven genotypes (GeneSeq) were ordered due to concerns about the emergence of resistant virus. In all but one case, providers at our site waited for two consecutively elevated VL measurements before ordering a genotype. Despite a previously reported mean VL of 2,947 copies/mL, none of these tests could be completed at the reference laboratory (Monogram Biosciences, San Francisco, CA) due to insufficient virus in the sample (less than 500 copies/mL). Although no costs were incurred from the reference laboratory for genotypes that could not be completed, there was a US $6.00 venipuncture/collection fee and these patients returned to clinic at earlier intervals than were typical in order to assess the suspected resistance to therapy.

The number of VL tests reported to be above the level of detection (50 copies/mL) increased dramatically after the introduction of the TaqMan VL assay. Despite no changes in ART, 46% of previously undetectable patients on stable ART regimens had a reported loss of virologic control following TaqMan implementation. Though other reports confirm the increased frequency of reported VL elevations with the TaqMan assay, this study is the first to quantify the economic impact of these findings. [7-10] We estimate 79 potentially unnecessary VL tests were ordered at our site among 198 newly “detectable” patients. The overall cost of additional laboratory testing exceeded US$20,000, a significant cost to the clinic, patients and/or third party payers. This conservative estimate does not take into account the increased workload and time required by clinic staff nor the economic and psychological impact on patients.

At our reference laboratory, the cut-off VL value to pursue genotypic testing is >500 copies/mL. A total of 62 patients had an initial elevated VL value reported by TaqMan above this threshold and 27 had a subsequent VL above this threshold. Our clinicians ordered seven genotypes among these patients. None of the requested genotypes were completed, because the samples had an insufficient amount of virus. After our clinicians became aware of the issues associated with the TaqMan assay, many decided to wait for additional elevated VL measures prior to ordering genotypic assays. Though this strategy may prevent the ordering of unnecessary genotype tests, it risks delay in detection of drug resistance in patients that are truly failing therapy, potentially leading to the accumulation of additional resistance mutations that may adversely impact subsequent treatment options.[12]

The findings of our study should be interpreted with respect to the limitation of the analysis. As a single-site cohort, the 1917 Clinic's experience with TaqMan may not reflect the experiences of other sites. Though we were unable to directly compare VL results of the TaqMan with the prior Amplicor assays by amplification of HIV RNA of the same specimen, the inclusion of subsequent TaqMan VL testing is a strength. An additional consideration that is as yet unresolved is whether the VL values reported by TaqMan reflect an increase in sensitivity and accuracy at the lower level of quantification or a limitation of this new assay.

The increased rates of detectable VLs observed following the implementation of the TaqMan assay, have led to increased costs to clinics, patients and/or third party payers, as well as,

increased workload for clinic staff. These costs exceeded $20,000 among our modest sample and would presumably be much greater across the HIV infected population undergoing TaqMan VL testing. Perhaps most important, but least quantifiable, is the psychological stress impacting patients and providers who must face an apparent loss of virologic control despite their best combined therapeutic efforts. Finally, delays in resistance testing due to uncertainty regarding the interpretation of TaqMan results may ultimately contribute to the accumulation of more resistance mutations, and negatively influence patient outcomes.

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References

1. Department of Health and Human Services. , editor. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretrovirals agents in HIV-1-infected adults and adolescents. 2008. p. 1-139.
2. Katzenstein DA, Hammer SM, Hughes MD, et al. The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cublic millimeter. N Engl J Med 1996;335(15):1091–8. [PubMed: 8813039]
3. O'Brien WA, Hartigan PM, Daar ES, Simberkoff MS, Hamilton JD. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. Ann Intern Med June 15;1997 126(12):939–45. [PubMed: 9182470]
4. Lin HJ, Myers LE, Yen-Lieberman B, et al. Multicenter evaluation of quantification methods for plasma human immunodeficiency virus type 1 RNA. The Journal of Infectious Diseases 1994;170(3):553–62. [PubMed: 7915748]
5. Katsoulidou A, Petrodaskalaki M, Sypsa V, et al. Evaluation of the clinical sensitivity for the quantification of human immunodeficiency virus type 1 RNA in plasma: Comparison of the new COBAS TaqMan HIV-1 with thre current HIV-RNA assays-LCx HIV RNA quantitative, VERSANT HIV-1 RNA 3.0 (bDNA) and COBAS AMPLICOR HIV-1 Monitor v1.5. Journal of Virological Methods 2006;131:18–174.
6. Oliver AR, Pereira SF, Clark DA. Comparative evaluation of the automated Roche TaqMan real-time quantitative human immunodeficiency virus type 1 RNA PCR assay and the Roche AMPLICOR version 1.5 conventional PCR assay. Journal of Clinical Microbiology 2007;45(11):3616–9. [PubMed: 17804650]
7. Damond F, Roquebert B, Benard A, et al. Human immunodeficiency virus type 1 (HIV-1) plasma load discrepancies between the Roche COBAS AMPLICOR HIV-1 MONITOR version 1.5 and the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assays. J Clin Microbiol 2007;45(10):3436–8. [PubMed: 17715371]
8. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. Clin Infect Dis 2009 Jan 15;48(2):260–2. [PubMed: 19113986]
9. Lima V, Harrigan R, Montaner JS. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. J Acquir Immune Defic Syndr 2009 May 1;51(1):3–6. [PubMed: 19247185]
10. Smit E, Bhattacharya S, Osman H, Taylor S. Increased frequency of HIV-1 viral load blip rate observed after switching from Roche Cobas Amplicor to Cobas Taqman assay. J Acquir Immune Defic Syndr 2009 Jul 1;51(3):364–5. [PubMed: 19553776]

11. Willig JH, Westfall AO, Allison J, et al. Nucleoside reverse-transcriptase inhibitor dosing errors in an outpatient HIV clinic in the electronic medical record era. Clin Infect Dis 2007;45:658–61. [PubMed: 17683005]

12. Peterson ML, Van der Laan MJ, Napravnik S, Eron JJ, Moore RD, Deeks SG. Long-term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. AIDS 2008;22(16):2097–106. [PubMed: 18832873]