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Research Article

Comparison of Two Molecular Tests, Roche COBAS®AmpliPrep/COBAS®TaqMan® and Abbott-RealTime in the HIV-1 Early Infants Diagnosis

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Abstract: *Background:* Prompt diagnosis and treatment of infants born to parents living with HIV is essential to reduce infant mortality. The availability of several high-throughput automated molecular tests is necessary to increase the services of early diagnosis tests in infants, especially in countries with limited resources such as Senegal. *Objective:* The objective of this study was to compare two automated molecular tests, Roche COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative and Abbott RealTime HIV-1 Qualitative in the early diagnosis of HIV-1 infection in children born to HIV-positive mothers in Senegal. Methods: The study was conducted exclusively at the molecular biology laboratory of the armed forces AIDS programme at the Ouakam Military Hospital, Dakar, Senegal, between September 2020 and December 2021. It involved 136 children aged between 1 and 18 months born to HIV-1 infected mothers. The samples were taken from blood obtained from the baby's heel, dried on blotting paper (DBS) and sent to the molecular biology laboratory. They were then stored at room temperature before being tested for the study. After these samples were analysed on both molecular techniques, the Abbott Qualitative results were compared to diagnostic tests performed with Roche COBAS®AmpliPrep/COBAS®TaqMan®HIV-1 Qualitative, which is the reference molecular technique. R Studio software version 099.902, 2016 was used to calculate specificity and sensitivity and Kappa coefficient. For statistical tests, they are considered significant when the P-value is less than 5%. *Results:* Out of a total of 136 samples tested, the overall positive and negative concordance was 94.84%, 79.41% and 93.58% respectively. The concordance coefficient, Cohen's Kappa coefficient, was also analysed. It gave a value of 0.853 (95% CI: [74.7-95.8]). A discrepancy was found between the two tests. Seven samples, which had previously tested positive on Roche Cobas, tested negative on Abbott Qualitative. *Conclusion:* The result showed a comparable performance characterized by very good negative, positive and global concordances and also, a very high Cohen's Kappa coefficient κ. The present study showed that the two molecular tests are comparable and that the Abbott Qualitative is a practical alternative for the diagnosis of HIV in infants.

Keywords: HIV-1-Early Infant Diagnosis, Roche COBAS®AmpliPrep/COBAS® TaqMan®, Abbott RealTime

1. Introduction

Since 1982, human immunodeficiency virus (HIV) infection has remained a major public health problem worldwide. In 2021, there were an estimated 38.4 million people living with HIV infection worldwide, including 1.5 million new infections [1]. In Africa, the most affected area is sub-Saharan Africa where girls and young women aged 15-24 are twice as likely to be living with HIV than young men with 63% of all new HIV infections in 2021 [1]. In Senegal, according to the 2021 annual report of the CNLS (National Council for the Fight against AIDS), the number of people living with HIV (adults and children) is estimated at 40277 people, including nearly 21703 women and 3957 children. under 15 years old. However, it has been found that new HIV infections are steadily declining. They fell from 5167 in 2005 to 1590 in 2021, i.e., a drop of 69.2% [2].

Although the prevalence of the latest Spectrum 2021 estimates shows a gradual decline in prevalence among 15–49-year-olds since 2005 from 0.75% to 0.32%, the 2021 CNLS annual report showed a significant feminization of the epidemic marked by a F/M ratio of 1.5 in people aged 15 and over [2]. Since there is a feminization of the disease, especially among young women of childbearing age, the risk of mother-to-child transmission of HIV is high [3]. Each year, nearly 1.5 million infants are exposed to HIV [4]. Most of them are infected by mother-to-child transmission [5]. This transmission can be antenatal, perinatal or horizontal [6] and remains an important public health problem. While new HIV infections among children have fallen by 41% since 2010, thousands of children get infected every year. Half of babies born with HIV who are not diagnosed early will die before their second birthday. Worldwide, only 59% of children exposed to HIV were tested within two months of birth [7]. Most of these children are on first-line treatment including lamivudine (3TC) and/or other molecules and the diagnosis is made very early in order to ensure better care. Early infant diagnosis is an important step in putting HIV-infected infants on antiretroviral therapy and reducing infant morbidity and mortality [8]. Indeed, the most widely used molecular test in the public health sector for molecular diagnosis is the Roche Amplicor HIV-1 DNA Test, version 1.5, a manual PCR DNA test [9]. However, it has been found that this test requires much more time (about 8h) with more manpower to obtain results [10]. Later, in 2007, Roche Diagnostic developed more automated, sophisticated and high throughput versions such as Roche Cobas Ampliprep/Cobas Taqman HIV for quantification of viral loads in people infected with the virus and Roche COBAS®AmpliPrep/COBAS®TaqMan® HIV-1 Qualitative for early infant diagnosis. Roche COBAS®AmpliPrep/COBAS®TaqMan® HIV-1 Qualitative has been evaluated by several laboratories for early diagnosis and is used in several countries on a large number of samples [11, 12, 13, 14]. Given the exponential demand for early diagnosis of HIV in infants, due to the persistence of mother-to-child transmission, several platforms of qualitative molecular tests for early diagnosis have been developed later, including the Abbott RealTime HIV-1 qualitative test. Although this molecular test has been developed, few studies on the evaluation of its performance characteristics have been carried out.

It is in this context that we evaluated the performance characteristics of the Abbott RealTime HIV-1 Qualitative Test compared to those of the COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Test for the early infant diagnosis. The objective of this study is to compare the performance of two molecular tests, the Abbott RealTime HIV-1 Qualitative and the COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative in HIV for the diagnosis of infants born to mothers living with HIV.

2. Material and Methods

2.1. Study Population and Samples

The study was conducted at the Molecular Biology Laboratory of the Armed Forces AIDS Program at Ouakam Military Hospital Dakar, Senegal, between September 2020 and December 2021. It involved 136 children aged between 1 and 18 months born to mothers infected with HIV-1. Patient information is collected on forms. Out of professional confidentiality and to protect patient privacy, the infants' identification and medical information was severed from the test results before they were used for the study. These children are received as part of the diagnosis of HIV in newborns for their biological follow-up in order to inform their mother of the HIV transmission or not of their babies. The samples are taken in different health structures in the country from the blood obtained from the baby's heel and dried on blotting paper, know as dried blood spot (DBS) and then sent to the molecular biology laboratory. DBS were stored at room temperature before being tested. These samples were passed through the two molecular diagnostic techniques COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative and Abbott Real Time HIV-1 Qualitative in order to compare their performance.

2.2. Molecular Tests

The COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Molecular Test which was first used in diagnosis is the gold standard and the Abbott-RealTime HIV-1 Qualitative Molecular Test should be evaluated.

2.2.1. COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative

The COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Test is a qualitative nucleic acid amplification test for the detection of HIV-1 RNA and proviral DNA in plasma, fresh anticoagulated whole blood and dried blood spots [15]. The test uses COBAS®AmpliPrep for extraction and COBAS®TaqMan 96 for real-time automated nucleic acid amplification and detection, respectively.

The COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Molecular Test is designed for the qualitative

detection of HIV-1 nucleic acid. It is a test that targets two HIV-1 sequences, the gag gene and the LTR of HIV-1 RNA. It includes three main steps: DBS pre-extraction, automated nucleic acid extraction, reverse transcription and PCR amplification. HIV-positive and HIV-negative DBS quality control samples were also analyzed alongside patient samples to monitor the DBS extraction/testing process. Reverse transcription, PCR amplification and detection of PCR products were performed by the Roche COBAS TaqMan (CTM) automaton according to the manufacturer's protocol. The result is presented as positive or negative.

2.2.2. Abbott-RealTime HIV-1 Qualitative

The Abbott real time HIV-1 Qualitative test is an in vitro molecular reverse transcription-polymerase chain reaction (RT-PCR) test for the detection of human immunodeficiency virus type 1 (HIV-1) [16]. It uses Abbott m2000sp for extraction and Abbott m2000rt for amplification respectively.

Abbott-RealTime HIV-1 qualitative is an in vitro real-time RT-PCR assay for the detection of HIV-1 nucleic acids in human plasma or DBS. It targets the pol gene of HIV-1. It also includes three main steps: pre-extraction, automated extraction of nucleic acids on the Abbott m2000sp machine and reverse transcription and PCR amplification on the Abbott m2000rt. HIV positive and negative DBS quality control samples were also included in each run for validation of nucleic acid extraction and amplification. For real-time RT-PCR amplification, nucleic acid extracts obtained after extraction were transferred to the Abbott m2000rt for amplification. The procedure was done according to the manufacturer's instructions.

2.3. Statistical Analysis

In an effort to assess the performance of molecular testing in early infant diagnosis between COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Comparatively and Abbott-RealTime HIV-1 Qualitative, data was collected in a spreadsheet Excel, Microsoft office Excel 2013 in order to be exploited. R Studio software version 099.902, 2016 was used to calculate specificity and sensitivity and Kappa coefficient. For statistical tests, they are considered significant when the P-value is less than 5%.

3. Results

3.1. Detection Rate Between COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative and Abbott-RealTime HIV-1 Qualitative

136 DBS samples were tested using the two molecular techniques, of which COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative is considered the reference technique. Of these 136 samples tested beforehand on Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative, 34 are positive, i.e. a rate of 25% of the sample. All samples were tested on Abbott-RealTime HIV-1 qualitative, 27 were positive giving a seropositivity rate of 19.85%. 7 samples were discordant, positive on Roche and negative on Abbott (Table 1).

Table 1. *Cross-Results Between Cobas and Abbott.*

Roche Cobas				
		Negative	**Positive**	**Total**
Abbott	Negative	102	7	109
	Positive	0	27	27
	Total	102	34	136

Table 2. *Agreement between Cobas and Abbott.*

Kappa de Cohen (K):	85.3% (IC à 95%: [74,7-95,8])
Overall agreement:	94.5%
Positive agreement:	79.4%
Negative match:	93.58%

3.2. Performance of COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative and Abbott-RealTime HIV-1 Qualitative in Early Infant Diagnosis

Out of a total of 136 samples, the two techniques agree on 129, for an overall agreement of 94.85%. The positive and negative agreements between the two are respectively 79.4% and 93.58% (Table 2). In order to confirm this good agreement between these molecular techniques, the coefficient of agreement, Cohen's Kappa coefficient k, was analyzed. Indeed, the two tests showed a good level of agreement with a Cohen's Kappa concordance correlation coefficient of 0.853 (95% CI; [74.7-95.8]) (Table 2). However, analysis of samples on both platforms revealed 7 discrepancies (detectable on Roche Cobas and undetectable on Abbott).

4. Discussion

Early infant diagnosis is an important step in evaluating the prevention of mother-to-child transmission of HIV and calls for important investigations into the performance of molecular techniques as these are increasingly available to meet the strong demand. Indeed, automated and reliable tests will allow reference laboratories to increase their capacities to test samples and return diagnostic results to clinicians as soon as possible. In addition, the use of automated tests could minimize the variability of results between different tests, and reduce human errors such as contaminations often occurring during manual manipulations and data transcription procedures [17]. However, few data on the evaluation of molecular test performance are available. In this study, the diagnostic performance characteristics of the Abbott Real Time HIV-1 Qualitative Test were evaluated by reference to those of the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Test.

Of a total of 136 samples previously tested on Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative, 34 were detectable, giving a seropositivity rate of 25%. Tested on Abbott afterwards, only 27 of the 136 are detectable, giving a seropositivity rate of 19.85%. The two molecular tests showed overall positive and negative agreements of 94.85%, 79.4% and 93.58% respectively. This overall concordance

(94.85%) is slightly lower than that found by Chang *et al* with an overall concordance rate of 99.5% [18].

It is important to emphasize that the sensitivity is calculated on the seropositive samples of the study referring to the positive concordance. Thus, the latter could then be compared to the sensitivities of other studies on the performance of these two tests to be studied. Indeed, the value found for the positive concordance is lower than the sensitivity found by Chang and his team in 2014 on an evaluation study of the qualitative test Abbott RealTime HIV-1 compared to Roche COBAS®AmpliPrep/COBAS® TaqMan® HIV -1 Qualitative for early infant diagnosis using dried blood drop samples and found a sensitivity of 99% (95% CI; [95-100]) [18]. The same is true for the study conducted by Zeh et al on an evaluation of these same molecular tests on dried blood drops (DBS) and dried plasma in Kenya and they found, for DBS, a sensitivity of 93.9% [95% CI: 88.8-97.2] [19]. Templer et al also found a higher sensitivity to this positive concordance (79.4%) on 100 DBS of HIV-positive infants tested on both Abbott and Roche tests with 100% concordance found [20]. Despite a slight difference in performance between the techniques, it is important to consider an assay of the amount of DNA from the extractions during the tests.

The two molecular tests showed comparable performance with a Cohen's Kappa coefficient κ = 85.3% (95% CI; [74.7-95.8]) indicating that they have excellent concordance (Cohen's Kappa value greater than 81% is interpreted as indicating excellent agreement [21]). This concordance coefficient is similar to that of Koné et al between the Xpert and Abbott test, comparing the performance of the Xpert HIV-1 viral load test and Roche TaqMan and Abbott m2000 RT in Mali [22]. This high concordance has been reported by several authors including Chang et al on a comparison study between Roche Cobas and Abbott on a set of 200 DBS samples [18]. A study from Botswana on the performance of the qualitative Cepheid Xpert® HIV-1 Point of Care test in newborns showed a sample that was seronegative on Xpert and seropositive on Roche TaqMan [23].

On the other hand, among the 136 samples tested on the two techniques, 7 samples are discordant. They are undetectable on Abbott and detectable on Roche Cobas. This discrepancy was also found by Chang et al where a seropositive sample obtained from Roche/Cobas was found seronegative from Abbott. According to Chang and colleagues, the mismatch does not appear to be due to a limited DNA concentration issue as other DBSs showing CT values of 26 by Roche's COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative all were detected by Qualitative Abbott [18]. According to this study, the mismatch could be caused by the loss of input DNA during the nucleic acid extraction process on the Abbott m2000sp. On the other hand, it is very difficult to explain how the nucleic acids of this single sample were lost during two separate extractions. Another possible explanation for this discordant result could be the differences in the primer/probe design of the COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Roche and Qualitative Abbott tests. According to the Roche package insert, the Roche COBAS®AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative test targets the gag and LTR region of the HIV-1 genome, while on the Abbott package insert, the Abbott Qualitative test targets the pol region. -integrase.

In perspective of our study, an increase in the sample size could give us more certainty regarding their performance.

5. Conclusion

This study evaluated the performance of the Roche COBAS®AmpliPrep/COBAS®TaqMan® HIV-1 Qualitative and Abbott RealTime HIV-1 Qualitative molecular test in samples from infants in Senegal. The latter showed a comparable performance characterized by very good negative, positive and global concordances and also, a very high Cohen's Kappa coefficient κ. Thus, Abbott could then be an effective alternative for the surveillance of the HIV virus in infants in a context with limited resources.

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