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The Diagnosis of HIV Infection in Infants and Children

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ABSTRACT

It is estimated that the number of HIV infected children globally has increased from 1.6 million in 2001 to 3.3 million in 2012. The number of children below 15 years of age living with HIV has increased worldwide. Published data from recent studies confirmed dramatic survival benefit for infants started anti-retroviral therapy (ART) as early as possible after diagnosis of HI. Early confirmation of HIV diagnosis is required in order to identify infants who need immediate ART. WHO has designed recommendations to improve programs for both early diagnoses of HIV infection and considering ART whenever indicated? It is strongly recommended that HIV virologocal assays for diagnosis of HIV have sensitivity of at least 95% and ideally greater than 98% and specificity of 98% or more under standardized and validated conditions. Timing of virological testing is also important. Infants infected at or around delivery may take short time to have detectable virus. Therefore, sensitivity of virological tests is lower at birth. In utero HIV infection, HIV DNA or RNA can be detected within 48 h of birth and in infants with peripartum acquisition it needs one to two weeks. Finally it is emphasized that all laboratories performing HIV tests should follow available services provided by WHO or CDC for quality assurance programs. Both clinicians and staffs providing laboratory services need regular communications, well-defined SOPs and nationally validated algorithms for optimal use of laboratory tests. Every country should use assays that have been validated by national reference laboratory.

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Introduction

It is estimated that the number of HIV infected children globally has increased from 1.6 million in 2001 to 2.1 million in 2008 and 3.3 million in 2012 in 2008 an estimated 430000 new HIV infections occurred in children whereas in 2012, 260000 children were newly infected with HIV (1-3). It is estimated that the number of children below 15 years of age living with HIV has increased worldwide (1-3).

Mother to child transmission (MTCT) of HIV is defined as transmission of HIV virus from HIV positive woman to the baby during pregnancy, labor and delivery or breastfeeding without prophylactic treatment (5-6). MTCT of HIV is an important cause of infection. Between 15% and 30% of infants born to HIV-positive women are infected during gestation and delivery while 5-15% is infected through Breastfeeding (3,

5-11). About 90% of new infections in children in 2008 acquired via MTCT by either labor and prepartum period or breastfeeding (12).

Data obtained from previous studies confirmed spectacular survival benefits for infants started anti- retroviral therapy as early as possible after HIV diagnosis (13-18). Early confirmation of HIV diagnosis is required in order to identify infants who need immediate ART (19-22). WHO has designed recommendations to improve programs for both early diagnoses of HIV infection and considering ART whenever indicated.

Diagnostic testing assays

Diagnostic testing procedures are needed to confirm the presence of HIV infection at any age. HIV serological procedures are often used to screen HIV exposure in infants, but they are also used as part of diagnostic tests in children aged over 18 months (23-26). When serological tests are used as screen method for HIV exposure, virological tests are recommended based on one reactive serological test (27). Serological testing identifies HIV antigen/antibody generated following immune response to HIV infection (28).

As we know maternal HIV antibody is transferred passively during pregnancy and decreases with the half-life of 28-30 d in non-breastfed infants (29-31). Most commonly used serological assays are not capable of differentiating between maternal HIV antibody or antibody produced by the infant, so other assays which detect the virus or its components are required to diagnose infection in this period (32-35). The mean/medium age at the time of seroversion ranges between 9-16 months in both developed and developing countries (36) and infants who have positive serological test at 9 months should have virological test to confirm the infection and identify infants who need anti-retroviral therapy (ART)(36).

Antibody to HIV can be measured by variety of techniques but since all these techniques detect an immune response to the virus, it takes some time to become reactive after infection.

ELISA is a serological test with high specificity and sensitivity that can help detect antibodies to both HIV1 and HIV2 (33, 37).

Selecting serological tests

Multiple factors should be considered in selecting serological tests including the commercial availability, cost of the test, training of staff, volume and type of the specimen required, laboratory quality assurance, specimen collection and processing and need for a cold chain in some circumstances (38).

WHO's description of generic testing algorithm is based on the purpose of HIV testing and prevalence of disease. In a high prevalence situation, the first positive test needs to be confirmed with another test with a different assay and two positive results will lead to HIV seropositivity (1-3, 39, 40).

If the second test is negative, the specimen needs a new testing by a third assay and in case the result is still non-reactive, the individual is seronegative (1-3). If the result of the third test is reactive, the individual should be referred for further testing in three weeks. In infants in relation to breastfeeding, the test can be interpreted after cessation of breastfeeding for 6 months. Therefore, in infant who is still breastfeeding, negative HIV test result cannot exclude HIV infection. In a low prevalence setting, again the first reactive test should be confirmed with a second assay (1-3). If the result of second test is non-reactive, the individual is HIV seronegative and if both tests are reactive, then a third different assay must be performed on the same specimen to confirm seropositivity and if the result of third test is non-reactive, the individual should be referred for further testing in three weeks (32).

WHO/UNAIDS define a generalized HIV epidemic as prevalence of =>1% in antenatal

clinic and for the purpose of selecting HIV testing strategies ,thresholds of =>5% in target population are suggested. The assays chosen are required to have or exceed sensitivity =>99% and specificity =>98% (3, 41-45).

Combination assays allow detection of P24, HIV antigen and HIV antibody and so have shortened window period (46). These rapid tests are available these days with diagnostic performance compatible to traditional EIA methods (sensitivity =>99%, specificity =>98%) and should be validated by national reference laboratory. They are quick, easy, cost-effective, require no equipment, there is lesser chance of error and the results are usually ready after 10-30 min (46-49).

The western blotting detect HIV antigen on a strip of nitrocellulose and the results can be interpreted as positive, negative and indeterminate (neither + nor – usually beginning of seroversion at the time of testing or cross reactivity) (1-3, 50). In this situation, test should be repeated 3 weeks later. Because western blot is sophisticated equipment and needs expertise in interpretation, today with improvement in performance characteristics of serological and virological tests it is no longer essential as a confirmatory test in HIV infection (50).

Virological testing detects presence of viral nucleic acid (i.e. viral RNA or viral DNA) or viral products such as P24 antigen. Most of these assays amplify genetic material of HIV and can be either qualitative or quantitative. PCR based techniques are the most widely used assays even in resource-limited settings (51-53).

In general, it is recommended to use HIV DNA on whole blood or dried blood spot (DBS), HIV RNA on plasma or DBS and ultrasensitive (US) P24 antigen on plasma or DBS. 500-1000 µl of plasma or serum is required for virological tests whereas DBS requires 25-100 µl whole blood. There is reasonable agreement between viral load results from plasma and DBS (47-48), however in plasma viral load (PVL) =<1000 copies/ml the DBS can represent higher results and lower limit of detection for DBS is 3000 copies/ml but this situation is only of concern when total suppression of HIV viral load is sought and for diagnosis in children who generally have higher viral loads than adults this will be problematic (53, 54).

It is strongly recommended that HIV Virological assays for diagnosis of HIV have sensitivity of at least 95% and ideally greater than 98% and specificity of 98% or more under standardized and validated conditions (55-57). HIV Virological tests should be used to diagnose HIV infection in infants and children below 18 month of age and all HIV-exposed infants should have virological testing at 4-6 weeks of age or at the earliest opportunity thereafter. It is strongly recommended that in infants with initial positive virological test, (ART) should be started without any delay and at the same time a second specimen should be collected for confirmatory test and it is not acceptable to delay ART while waiting for result of confirmatory test (58-59).

HIV DNA could be recognized in the blood mononuclear cell and lymphoid tissue of HIV positive children who have received anti-retroviral drugs (41, 60- 67). RNA detection in plasma seems is sensitive during the first couple of weeks of life (61, 68- 70). Despite the association of administration of maternal ART with reduced replication of HIV, studies have in general shown no loss of sensitivity (41, 42, 44, 69, 71). Some of the newer molecular assays detect both DNA and RNA in whole blood. Increased sensitivity and reduced window period are the main advantages (48, 51, 66).

P24 assays measure HIV core P24 in whole blood, serum or plasma. When antibody to HIV becomes detectable, P24 antigen is no longer demonstrable. Available data suggest that US P24 is better to be used up to 18 months of age and the sensitivity may decline with increasing age. Since detection of P24 antigen depends on viral replication and ART inhibits this, there

are some concerns that US P24 detection assays are not suitable when the mother or infant is on ART. HIV RNA and HIV DNA testing are recommended in these circumstances (54, 61).

Recently technical improvements have enabled the newer immune complex-dissociated US P24 test that can be performed as well as HIV DNA PCR in diagnosis of HIV in infants and can be done in laboratories that can perform EIA testing. These tests are less complex and less costly and can be performed on whole blood, plasma or DBS with no need for nucleic acid extraction (32, 66).

General factors that should be considered in virological tastings are commercial availability, equipment required for performance and handling, costs, number of specimens, specimen storage and transport and ongoing laboratory quality control (64). The timing of virological testing is also important. Infants infected during delivery may take short time to have detectable virus. Therefore, the sensitivity of virological tests is lower at birth (3).

In utero HIV infection, HIV DNA or RNA can be detected within 48 h of birth but in infants with peripartum acquisition it needs one to two weeks. Generally, by six weeks of age almost all infants can be identified by virological tests (1-3). Disease progression is rapid in young infants, so the turned around time from specimen collection to giving results should not be more than 4 weeks. If HIV infection is considered as underlying cause of symptoms and signs in sick infants and virological tests are not available, using serological testing accompanied by clinical algorithm is strongly recommended. Point of care assays are under evaluation and could offer many advantages in near future (1-3, 33, 67).

Regarding breastfeeding, it is recommended that breastfeeding should not discontinue in order performing of diagnostic tests (51). A positive virological test in the presence of breastfeeding indicates infection and should prompt confirmatory tests, but negative virological tests as long as exposure to HIV is continuing are not reliable and conduction of virological tests after 6 weeks of cessation of breastfeeding is indicative of the HIV status (46, 61, 69-71).

Another important point related to HIV virus is the diversity of HIV which means that molecular methods for identification of HIV DNA and RNA require constant monitoring and assessment. Commercial serological EIAs appear to detect most subtypes and groups of HIV and new rapid assays can also detect HIV1 and HIV2 with accuracy comparable with EIAs (3, 28). Cell culture is no longer recommended for diagnosis of HIV because of complexity, biosafety and costs (43).

Conclusion

Finally, it is emphasized that all laboratories performing HIV tests should follow available services provided by WHO or CDC for quality assurance programs. Both clinicians and staffs providing laboratory services need regular communications, well-defined SOPs and nationally validated algorithms for optimal use of laboratory tests. Non-commercial tests are not recommended for widespread use by national programs. Every country should use assays that have been validated by national reference laboratory.

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