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DIAGNOSTIC PATTERNS OF RAPID TESTS USED FOR DETECTING HIV INFECTION IN KAZAKHSTAN

Abstract. This article presents the results of the comparative analysis of sensitivity and specificity of five express test systems used in Kazakhstan to detect the markers of HIV infection. Currently, there are several express test-systems for HIV detection that are officially licensed for use in Kazakhstan. These are the following: «Alere Determine HIV ½ Ag/Ab Combo»; «Hexagon HIV 1+2»; «Abon HIV ½»; «HIV 1,2 Han Medtest»; «Geenius HIV ½ Confirmatory». The diagnostic systems listed above are fully compatible with current WHO requirements (sensitivity >99%, specificity >98%). The validation study results clearly indicate that these test systems can be used in Kazakhstan as a rapid HIV testing procedure for the key population groups conducted by the non-governmental organizations. The diagnostic characteristics obtained from the investigation of these express HIV tests could serve as a background information for the development and approval of the national standard protocols for rapid HIV testing in Kazakhstan.

Keywords: HIV infection, express tests, sensitivity, specificity, non-governmental organizations.

Currently, HIV infection and AIDS has acquired a global dimension. According to the report of the Joint United Nations Program on HIV/AIDS (UNAIDS), published in 2016 [1], around 36.7 million people in the world are HIV-positive, among them 17.8 million women and 2.1 million children under the age of 15.

As of 1 January 2018, the Republican AIDS Prevention and Control Center of the Ministry of Health of the Republic of Kazakhstan reported the total of 32,573 accrued HIV cases in the country. The total number of people living with HIV (PLHIV) is reported to be 20,841 with the prevalence of PLHIV per 100,000 of 117.7. The highest prevalence rates for PLWH were noted in Northern and Eastern Kazakhstan, Pavlodar, Karaganda and Kostanay regions as well as in Almaty and Astana cities [2].

The above-mentioned statistics provide clear evidence of a complex epidemiological situation regarding the HIV infection in the country: a high incidence rate coupled with a slow decrease of new HIV cases.

In this regard, timely detection of HIV infection, implementation of new diagnostic methods and improvement of existing ones are the key priority areas in accelerating the fight against HIV/AIDS epidemic in Kazakhstan. Currently, the World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS) recommended a 90-90-90 treatment target, which stipulates that 90% of people living with HIV should be diagnosed; 90% of diagnosed people must be on antiretroviral therapy; 90% of treated people should be virally suppressed [3]. In order to reach the 90-90-90 target, WHO and UNAIDS recommend that the rapid HIV testing methodology to be administered by the non-governmental organizations as key target population groups use the services of non-governmental organizations [4]. The key target groups include: men who have sex with men (MSM), injecting drug users (IDUs), sex workers, people in penal institutions and transgender persons. In order to significantly scale-up the access to HIV prevention, treatment, care and support programs, it is important that the key target population know their current HIV status. The literature indicates that [5] the efficacy of rapid HIV

tests is roughly comparable to that of Enzyme Immunoassay and Western blot methods. Moreover, the rapid HIV testing systems proved to be an important diagnostic tool where laboratories have limited facilities or where technicians have no lab-specific training. Currently, there are also different test systems for rapid HIV diagnostics that are widely available, such as the lateral flow immunoassay tests, the flow meters and trays for agglutination etc. These systems allow to determine one's HIV status within 15-20 minutes in whole blood, serum, plasma and saliva. Apart from that, for some tests, there is no need to dilute the reagents or refrigerate them. Moreover, they are easy to use and with a minimum amount of equipment or no equipment at all. Tests can be stored at contact temperature.

However, the lack of standards for diagnostic systems for the rapid HIV diagnostics in many countries has led to extensive use of non-standard, low quality test systems. Therefore, the World Health Organization (WHO) recommends conducting an assessment of the quality parameters of rapid HIV tests, especially before they begin to use [6]. In Kazakhstan, as noted by the specialists of the Republican AIDS Prevention and Control Center [7], there are ten rapid HIV tests that have been officially registered. However, in practice, they are only used for testing certain population groups and the results are only considered as preliminary. A confirmation of preliminary results by the traditional enzyme immunoassay methods is required. Additionally, the lack of research in Kazakhstan on important diagnostic parameters such as sensitivity and specificity of HIV rapid tests used in the country do not allow the development of national rapid HIV testing protocols that guarantee high reliability and accuracy of HIV detection.

The aim of this work is to conduct a comparative analysis of the sensitivity and specificity of rapid HIV tests used in Kazakhstan.

Materials and methods. The study was carried out at the diagnostic laboratory of the Republican AIDS Prevention and Control Center. The following materials were used in assessing the quality parameters of rapid tests:

1. Five different types of licensed express HIV tests provided by five companies registered in Kazakhstan were made themselves available for this assessment. In particular, the following test systems have been included in this research:

a) Alere Determine HIV ½ Ag/Ab Combo;

b) Hexagon HIV 1 + 2;

c) Abon HIV ½;

d) HIV 1,2 Han Medtest;

e) Geenius HIV ½ Confirmatory.

2. Serum sample collection prepared at the Republican AIDS Center's laboratory which consists of 300 HIV-positive and 300 HIV-negative samples. The lab-samples from HIV-negative set were given the registration numbers 1 through 300, whereas HIV-positive samples were assigned from 301 to 600.

3. A panel of titrated serum samples of human blood consisting of 100 samples prepared by diluting 10 HIV-positive samples in a pool of HIV-negative serum. These samples were made at the diagnostic laboratory of the Republican AIDS Center by a series of 4-fold dilutions and were assigned from 601 to 700.

Interpretation of the panel testing results was done in the following ways: samples of both panels were tested by two ELISA test: Genscreen UltraHIV Ag-Ab (Bio-Rad, France) and Murex HIV Ag/Ab (DiaSorin, Italy).

The samples were considered as «negative» when both of the ELISA and immunoblot tests turned out to be non-reactive. The samples that had inconsistent or uncertain results were excluded from the further research.

Each sample was tested by five rapid tests. The sensitivity, specificity and prognostic value of «positive» and «negative» results of each rapid test were calculated on the basis of comparison with the results of the confirmatory test using the 2x2 table and retrospective data on the prevalence of HIV infection among the population groups. To calculate the sensitivity and specificity of the test, only those samples that had been determined as a «positive» or «negative» in the results of testing by «gold standard» (ELISA-ELISA- immunoblot) were used.

To assess the quality parameters of the rapid tests, a WHO methodology for the similar studies was used [6, 8]. During the statistical processing, the 95% confidence interval for binomial ratios was calculated based on Fisher's F distribution at a ratio tending to 1.0 [9].

The statistical analysis was conducted by using the *Statistical Package for Social Science* (SPSS) - an international standard for processing of statistical information.

Results and discussion. This research has explored the sensitivity and specificity of each rapid test. Also, some traditional features of testing systems were examined. The summary results of evaluation of each test system are provided below.

1. *Alere Determine HIV ½ Ag / Ab Combo*

– The first set of tests of this diagnostic system on the panel containing 600 native serum samples revealed all HIV-positive samples.

– Two false-positive results were recorded in testing HIV negative specimens N63 and N120. The first-degree clinical sensitivity was 100% (98.78% - 100%), clinical specificity - 99.33% (97.61% - 99.92%).

– In the second set of testing all samples were identified correctly. The sensitivity was 100% (98.78% - 100%), as well as the specificity (98.78% - 100%). The coefficient of variability of the results was 0.33%.

– On the panel of titrated samples, the test had an all- positive reaction in the samples with a dilution of 1/256.

Conclusion. The quality parameters of both testing sets, namely, Alere Determine TM HIV ½ Ag / Ab Combo, meet WHO requirements.

2. *Hexagon HIV 1 + 2*

– The first series of the test system on the panel of samples resulted in one false-negative (sample N454) and one false-positive (N215) outcome. The sensitivity and specificity were 99.67% (98.16% - 99.99%).

– The sensitivity of the second set of tests was 100% (98.78% -100.00%), and specificity - 98.33% (96.15% -99.46%). The coefficient of variability between the series was 0.83%.

– The study of the characteristics of the test with the panel of titrated samples revealed antibodies to HIV in all samples with a dilution of 1/256.

Conclusion. The quality parameters of both Hexagon HIV 1 + 2 series are in line with WHO recommendations.

3. *Abon HIV ½*

– During the test of the first series of this diagnostic system using the panel of native samples, all HIV-positive and HIV-negative samples had been identified with an exception of one invalid sample (specimen N502). The sensitivity was 100% (98.77% -100.00%), the same level specificity has also been determined - 100% (98.78% -100.00%).

– The test of the diagnostic system using the panel of titrated samples showed that the analytical sensitivity of the second series of the diagnostic test system are slightly higher than in the first series. The variability of the results between series was 0.33% and the invalid indication was 0.17%.

Conclusion. Both series of the test system Abon HIV ½ meet WHO requirements.

4. HIV 1,2 Han Medtest

– The evaluation of the first series of this test system using the panel of native samples revealed high quality features: the sensitivity was 100% (98.78% -100.00%), the specificity was also 100% (98.78% - 100.00%).

– However, in the process of assessing the second test series, 12 false-positive results were obtained (samples N: 68, 94, 96, 98, 100, 101, 102, 103, 106, 115, 195, 280). The sensitivity was 100% (98.78% - 100.00%) and the specificity was 96% (93.12% -97.92%).

– The coefficient of variability in the results between two series was 2%, which according to the WHO criteria it is at the borderline of acceptability of diagnostic testing.

– The analytical sensitivity of the second series of this test system also turned out to be lower: antibodies were detected only at the dilution of 1/16.

Conclusion. The quality parameters of the HIV 1.2 Han Medtest system meet the minimum standards of WHO.

5. *Geenius HIV ½ Confirmatory*

– The test of the first series on the panel of native samples has identified nearly all the HIV-positive and HIV-negative samples correctly, except for one lab sample (N. 90). The sensitivity was 100% (98.78% -100.00%), the specificity was also 100% (98.77% -100.00%)

– The variability index of the results from two series was 0.5%, invalid feature - 0.17%.

– Evaluation results with titrated panel showed that the test system detected antibodies in all samples with a titer of HIV-1/64.

Conclusion. The quality parameters of both kits of the Geenius HIV ½ Confirmatory system meet WHO requirements.

The results achieved during the investigation confirmed that the researched HIV rapid tests used in Kazakhstan fully meet WHO standards for the following quality parameters: sensitivity and specificity (sensitivity> 99%, specificity> 98%). It should be noted, that the first series of the HIV-1,2 Han Medtest (Kazakhstan) rapid diagnostic system showed the highest sensitivity and specificity (i.e. 100% and 100%). However, the second series of the same test system showed the low specificity (96%), which is below the acceptable standards set by WHO. Thus, a local producer, perhaps, need to make a major effort to standardize the manufacturing process of the test system.

During the implementation of the rapid HIV testing centers based in non-governmental organizations in Kazakhstan, the following WHO recommendations should be used to select the diagnostic systems [6]. In a context of limited resources, the standard procedure for determining the product (test system) quality should focus on the following three main areas:

1. Safety assessment and quality verification of the analytical efficacy of the test system as per manufacturer's description.
2. Desk review of quality management systems used in the production of test systems.
3. Independent Laboratory Evaluation of diagnostic characteristics of the rapid tests.

Conclusion. The researched test systems for the rapid HIV diagnostics (Alere Determine TM HIV ½ Ag/Ab Combo, Hexagon HIV 1 + 2, Abon HIV ½, HIV 1,2 Han Medtest, Geenius HIV ½ Confirmatory) completely meet the standard requirements of WHO and can be used in Kazakhstan for rapid HIV testing of the target groups in non-governmental organizations' settings.

The diagnostic characteristics obtained from the researched rapid HIV tests could serve as a background information for development and approval of the national standard protocols of rapid HIV testing in Kazakhstan.

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ҚАЗАҚСТАНДА АИТВ-ЖҰҚПАСЫН ДИАГНОСТИКАЛАУДА ҚОЛДАНЫЛАТЫН ЖЕДЕЛ-СЫНАҚТАМАЛАРДЫҢ ДИАГНОСТИКАЛЫҚ СИПАТТАМАСЫ

Аннотация. Мақалада АИТВ-жұқпасының маркерін анықтауға арналған Қазақстанда қолданылатын бес жедел-сынақтамалардың сезімталдылығын, ерекшелігін зерттеудің нәтижелері көрсетілген. Қазақстанда ДДСҰ талаптарына сәйкес келетін АИТВ-ны жедел-диагностикалауға лицензияланған бірнеше тест-жүйелер бар. (сезімталдық >99%, ерекшелік >98%). Бұл: Alere Determine ™ HIV ½ Ag/Ab Combo; Hexagon HIV 1+2; Abon HIV ½; HIV 1,2 Han Medtest; Geenius HIV ½ Confirmatory. Валидациялық зерттеулердің нәтижелері бойынша үкіметтік емес ұйымдардың негізінде тұрғындардың осал топтары арасында АИТВ-ға жедел-сынақтама жүргізу үшін көрсетілген тест-жүйелер Қазақстанда қолданылуы мүмкін. АИТВ-жұқпасын анықтау үшін зерттелетін жедел-сынақтамалардан алынған диагностикалық сипаттамалар АИТВ-ға тестілеудің халықаралық алгоритмі Қазақстанда әзірлеу мен бекітуге базалық ақпараттық материал болып қызмет атқаруы мүмкін.

Түйін сөздер: АИТВ-жұқпасы, жедел-сынақтама, сезімталдық, ерекшелік, үкіметтік емес ұйымдар.

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ДИАГНОСТИЧЕСКИЕ ХАРАКТЕРИСТИКИ ЭКСПРЕСС-ТЕСТОВ, ИСПОЛЬЗУЕМЫХ ПРИ ДИАГНОСТИКЕ ВИЧ-ИНФЕКЦИИ В КАЗАХСТАНЕ

Аннотация. В статье представлены результаты сравнительно изучения чувствительности, специфичности пяти экспресс-тестов, используемых в Казахстане для выявления маркеров ВИЧ-инфекции. Отмечено, что сегодня в Казахстане несколько лицензированных тест-систем для экспресс-диагностики ВИЧ, которые полностью отвечают современным требованиям ВОЗ (чувствительность >99%, специфичность >98%). Это: Alere Determine ™ HIV ½ Ag/Ab Combo; Hexagon HIV 1+2; Abon HIV ½; HIV 1,2 Han Medtest; Geenius HIV ½ Confirmatory. Результаты валидационного исследования свидетельствуют, что данные тест-системы могут быть использованы в Казахстане для проведения процедуры экспресс-тестирования на ВИЧ среди ключевых групп населения на базе неправительственных организаций. Полученные диагностические характеристики исследуемых экспресс-тестов на выявление ВИЧ-инфекции могут служить базовым информационным материалом для разработки и утверждения в Казахстане национальных алгоритмов тестирования на ВИЧ с использованием экспресс-тестов.

Ключевые слова: ВИЧ-инфекция, экспресс-тесты, чувствительность, специфичность, неправительственные организации.

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