SCREENING FOR HIV INFECTION DURING THE REFUGEE DOMESTIC MEDICAL EXAMINATION

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Key Points

Post-arrival screening:

- Beginning January 4th, 2010, refugees are no longer tested for HIV-infection prior to arrival in the U.S.
- Current CDC guidelines for the United States recommend HIV screening in health-care settings for all persons 13-64 years of age [1]. Screening of all refugees 13-64 years of age is recommended in accordance with this policy. Screening of all refugees on arrival, including those ≤12 years and ≥64 years of age, is also encouraged.
- Repeat screening 3-6 months following resettlement is recommended for refugees with a recent exposure or high-risk activity to identify individuals who may be in the "window period" when they arrive in the United States. Subsequent screening should be done in accordance with CDC guidelines.
- Specific testing for HIV-2 should be conducted for refugees who screen positive for HIV and are native to or have transited through the following countries: Angola, Benin, Burkina Faso, Cape Verde, Côte d'Ivoire (Ivory Coast), Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Mozambique, Niger, São Tomé, Senegal, Sierra Leone, and Togo.
- Screening should be performed on all refugees unless they decline (opt out). Refugees should be clearly informed orally or in writing that HIV testing will be performed. Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as other screening or diagnostic tests. Where separate consent is mandated by State law, a separate consent form for HIV testing must be utilized. (A compendium of requirements in specific jurisdictions is available at http://nccc.ucsf.edu/.)
- Efforts should be made to understand the context of HIV testing, diagnosis, and care within specific cultural and societal norms. Information about HIV and HIV testing should be provided in the languages of the commonly encountered populations within the service area. The competence of interpreters and bilingual staff to provide language assistance to patients with limited English proficiency must be ensured.
- When a refugee declines an HIV test, this decision should be documented in the medical record.
- All HIV-infected individuals should receive culturally sensitive and appropriate counseling in their primary spoken language.
- Appropriate referral for care, treatment, and preventive services should be made for all individuals confirmed to be HIV-infected.

Special pediatric considerations:

- Children <13 years of age should be screened unless negative HIV status for the mother of the child can be confirmed and the child is otherwise thought to be at low risk of infection (no history of high-risk exposures such as previous blood product transfusions, early sexual activity, or history of sexual violence or abuse). In most situations, complete risk information will not be available, and thus most children <13 years of age should be screened.

- Children <18 months of age who test positive for HIV antibodies should receive further testing with DNA or RNA assays. Results of positive antibody tests in this age group can be unreliable because they may detect persistent maternal antibody.
- All children born to or breast-fed by an HIV-infected mother should receive chemoprophylactic trimethoprim/sulfamethoxazole beginning >6 weeks of age until they are confirmed to be uninfected.

Special considerations for pregnant women:

- The identification and treatment of HIV-infected pregnant women can prevent HIV infection in their infants. All refugee women who are pregnant should undergo routine HIV screening as part of their post-arrival and prenatal medical screening and care.

Background

The Global Burden of HIV

The HIV/AIDS pandemic remains one of the most serious global health challenges today [2, 3]. More than 30 million people were living with HIV at the end of 2007, with approximately 2.1 million deaths annually due to AIDS [2]. In addition, an estimated 2.7 million new HIV infections occurred in 2007 [2]. While HIV/AIDS affects individuals throughout the world, certain regions, such as sub-Saharan Africa, have disproportionally high prevalence rates (exceeding 20% in some countries). In addition, HIV/AIDS disproportionately affects certain vulnerable population groups, such as young adults, women, and children.

Refugees and HIV infection

The increasing global rates of new HIV infections, despite efforts in prevention, coupled with the increasing mobility of populations, make HIV/AIDS an important issue in every country. Although the link between HIV and migration is complex and nonlinear, multiple factors heighten the HIV risk for refugees. Economic distress, conflict, sexual abuse and violence, oppression, discrimination, exploitation, gender bias, and sociopolitical marginalization contribute to conditions in which transmission of HIV may be enhanced [4, 5]. However, few studies have been performed that document actual increased risk behaviors in specific refugee populations [5]. In addition, refugees are frequently excluded from the national health care systems of host countries where they reside, and, until recently, voluntary counseling and testing (VCT) was not provided in many camp settings or to urban refugee populations [6,7]. Even when VCT is available, many barriers may exist for refugee populations that make testing less accessible (e.g., mistrust in how asylum countries may use information, difficulty in maintaining confidentiality in refugee settings) [8].

Approximately 14% of the incoming refugees to the United States arrive from countries with HIV prevalence >5% [9-11]. These figures are based on country-specific HIV prevalence data from the end of 2006 and may underestimate true infection rates because of underreporting or lack of surveillance data. In addition, prior to resettlement, refugees may have traveled to or lived in other countries with high HIV prevalence rates. Refugees may also have been victims of physical and sexual violence and may be at risk of HIV acquisition through rape, blood product transfusions, or other medical procedures leading to infection, or through drug use [12-14]. Disclosure of these exposures may not be forthcoming during initial intake assessments. It is imperative that a scientific and rational approach to the screening, diagnosis, support and care of these individuals be developed and implemented.

Pre-departure medical screening

Prior to departure to the United States, all refugees undergo a pre-departure medical screening process. This process generally includes screening for inadmissible medical conditions (e.g., active tuberculosis), as well as presumptive pre-departure treatment for malaria and intestinal parasites, when appropriate. HIV has been removed from the list of inadmissible conditions, and refugees are no longer routinely tested for HIV prior to departure to the United States.

HIV screening during the domestic medical screening examination

Identifying HIV infection has implications for the individual refugee, the clinical provider, and the public health system. Early entry into care and treatment for HIV has been associated with improved survival [15]. The use of highly active antiretroviral therapy (HAART) has led to substantial declines in morbidity and mortality experienced by HIV-infected persons. In addition, knowing one's HIV status has important implications for the prevention of transmission to others.

Studies specifically examining the cost-effectiveness of screening refugees in the era of HAART in the United States are currently lacking. However, the cost-effectiveness of routine HIV screening in health-care settings is comparable with that of other commonly accepted screening interventions, even in populations with relatively low seroprevalence [16, 17]. The current guidance from CDC recommends testing for HIV as a routine part of medical care and stresses an "opt out" approach in which a patient is notified that testing will be performed unless the patient declines [1]. The current CDC guidelines are available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm.

Considerations for testing

Testing for HIV infection has historically been complicated by the diversity of the HIV genome and the inability of various assays to detect all types and subtypes of HIV. Currently, available assays are largely able to overcome these limitations, although an understanding of both population differences and variability in assay performance is important.

Two types of HIV are known to infect humans: HIV-1 and HIV-2. HIV-1 is the cause of the majority of HIV infections globally [18]. HIV-2 accounts for less than 1% of HIV infections worldwide and is found mostly in West Africa, although cases have been reported from India, Europe, Brazil, and the United States [19]. While most available tests in use in the United States screen for both HIV-1 and HIV-2, specific testing for HIV-2 infection should be performed in individuals from areas where HIV-2 is common, if their HIV screening test is reactive.
HIV-1 is divided into three groups: Group M (major), Group N (nonmajor), and Group O (outlier) [20,21]. Group O is found in West and Central Africa and is of particular importance to HIV screening, as some assays fail to detect Group O infections. Group M constitutes 90% of current HIV infections and is further divided into phylogenetically distinct subtypes (A1-4, B, C, D, F1-2, G, H, J and K) [22]. Subtype B, found predominantly in the United States and Europe, has been the most studied subtype, although it represents less than 12% of worldwide infections. Globally, the most prevalent subtype is C, constituting half of all known infections. See below for a table of geographic distribution of subtypes [22].

Subtype	Location	Proportion of known infections
A	East and Central Africa, central Asia, eastern Europe (including Russia)	12.3%
B	Americas, Western Europe, East Asia, Oceania (including Japan)	10.2%
C	India, Nepal, Eastern and Southern Africa	49.9%
D	East and Central Africa	2.5%
G	West Africa, East Africa, Central Europe	6.3%
F, H, J, K	Various locations	<1% each
Circulating recombinant forms (CRFs)	Various locations	remainder

Available testing methods

Conventional Antibody Testing

EIA test results are classified as reactive or nonreactive. Specimens with a nonreactive result from the initial EIA are considered HIV-negative. Specimens with a reactive EIA result are retested in duplicate. If the result of either duplicate test is reactive, the specimen is reported as repeatedly reactive and undergoes confirmatory testing with a more specific supplemental test such as Western blot, immunofluorescence assay (IFA), or RNA testing [26]. Some laboratories report only a final result (not an initial reactive EIA result that is not confirmed). This reporting may have implications, particularly for individuals with very recent infections or for Group O infections.

The HIV-1 Western blot is a solid-phase EIA with immobilized viral antigens to detect IgG antibodies to specific HIV proteins. A Western blot is interpreted as positive if bands appear at the site of two or more of the following HIV antigens: p24, gp41, or gp120/160. Specimens that are repeatedly reactive by EIA and Western blot are considered HIV-positive. The Western blot is considered indeterminate if bands are present, but fewer than two of the latter bands are present. Specimens that are repeatedly EIA-reactive occasionally provide an indeterminate Western blot result, due either to an incomplete antibody response to HIV in an infected person or to nonspecific reactions in an uninfected person [27]. The Western blot is interpreted as negative only if no bands are present. Repeat Western blot or RNA testing, performed on a subsequent blood specimen, will distinguish persons with early infections from uninfected persons with persistent indeterminate results.

Current HIV EIAs are >99% sensitive and specific for HIV infection and are able to detect nearly all non-B subtypes and most group O infections [28]. However, Western blot may fail to

detect group O in 10%-20% of specimens [29]. Individuals from areas with high rates of group O infection (e.g., Cameroon) with reactive EIAs but a negative Western blot should undergo further testing with assays known to detect group O (RNA testing).

Rapid Diagnostic Tests

Diagnostic testing for HIV also includes rapid antibody assays, whose sensitivity and specificity are high ($\geq$ 99%) [31, 32]. Rapid tests may be particularly useful for screening individuals who may not return for the results of conventional screening tests. A rapid antibody test produces results in 20 minutes or less. Six FDA-approved rapid tests detect the presence of antibodies to HIV in blood, serum, or oral fluid specimens [33]. As with the conventional EIA, a reactive rapid HIV test result must be confirmed with a follow-up supplemental test (e.g., Western blot or RNA) before a final diagnosis of HIV infection can be made [33]. If confirmatory testing yields negative or indeterminate results, follow-up testing should be performed on a blood specimen collected 4 weeks after the initial reactive rapid HIV test result. Most rapid HIV-1 tests are capable of detecting all major subtypes of group M, although not all rapid HIV screening assays detect Group O. Four rapid tests are FDA-approved for detection of both HIV-1 and HIV-2, one of which can differentiate HIV-1 from HIV-2 [30].

Nucleic Acid Tests

A qualitative RNA test has been FDA-approved for diagnosis of acute HIV infection in antibody-negative persons. This test may also be used to confirm a reactive antibody screening test. Quantitative tests for HIV RNA are available, but are not FDA-approved for diagnosis. These RNA tests are routinely used to quantify viral load for monitoring progression of HIV disease [33]. HIV-1 RNA tests do not detect HIV-2, and the FDA has not approved an HIV-2 RNA or DNA test [30]. Plasma viral load is characteristically low in HIV-2 infection and RNA testing is unreliable for the detection of HIV-2. DNA testing for HIV-2 can be performed to confirm HIV-2 infection.

Pediatric screening considerations:

HIV disproportionately affects children of foreign-born mothers [34]. A 2002-2003 report of the Ministerial Council on HIV/AIDS in Canada estimated that 70% of all maternal HIV transmission to children in Canada occurred among women of African and Caribbean origin [34]. Despite HIV disease progression being more rapid in children and data suggesting that infected children have significantly improved survival when antiretroviral therapy is initiated early, HIV screening in children <15 years of age has often been restricted to those with identifiable risk factors (receipt of blood products, HIV-infected mother, or other risk factors identified by provider).

The diagnosis of HIV in children is complicated by the presence of passively acquired maternal anti-HIV immunoglobulin (IgG) in children born to HIV-infected mothers. Maternal antibody has been demonstrated in children up to 18 months of age, complicating interpretation of positive antibody test results [35]. The American Academy of Pediatrics recommends that infants born to HIV-positive mothers undergo DNA or RNA testing at day 14, again at 1-2 months of age, and then at 3-6 months of age. A positive RNA or DNA result at any age is a presumptive indicator of HIV infection but must be confirmed. The diagnosis of a HIV-infection is made if two DNA or RNA tests are positive. CDC guidelines state that HIV is definitively excluded by two negative RNA or DNA tests (at 1 month and >4 months) or two negative antibody tests from

separate specimens obtained at age >6 months. Given that HIV can be transmitted from mother to child through breastfeeding, many clinicians confirm the absence of HIV-1 with a negative HIV-1 antibody assay at 12-18 months of age or after the child is no longer breastfeeding [35].

Summary:

Refugees represent a population vulnerable to HIV infection and disease. Given the known benefits of early detection, counseling, provision of antiretroviral therapy, and prevention of mother-to-child transmission, HIV screening should be offered to all refugees resettling in the United States.

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