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The Evolving Landscape of HIV Screening in the Emergency Department

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More than 1.1 million individuals are infected with HIV in the United States, and until recently, the proportion of infections that were undiagnosed had remained relatively high (21%) and unchanged.^{1,2} Recognizing that individuals with undiagnosed HIV infection were contributing significantly to incident cases, the Centers for Disease Control and Prevention and the US Preventive Services Task Force invoked new and more aggressive screening recommendations.^{3,4} These, coupled with a comprehensive national plan by the Office of National AIDS Policy, and broad and sustained implementation efforts by a wide variety of academic, public, and industry partners, have led to substantial progress at reducing the number of individuals with undiagnosed HIV infection, now estimated to be 13% of all those infected with HIV.^{5,6}

Testing for HIV infection remains the first in a series of important interventions aimed at closing the undiagnosed gap, and emergency department (ED)–based screening for HIV infection has contributed significantly.^{7–9} Identifying individuals with HIV infection provides a critical opportunity to link them into care where treatment effectively slows disease progression and infectivity.^{10,11} Furthermore, knowing one's serostatus attenuates individual behaviors that contribute to transmission of the virus.¹²

In this issue of *Annals*, 2 important studies are reported, both of which collectively advance our understanding of HIV identification in EDs and frame the future of ED- based HIV screening.^{13,14} Both studies demonstrate different but important methodological approaches

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—a large-scale program evaluation and a multicenter pragmatic clinical trial—critical when informing practice and policy.

The article by White et al¹³ reports a multicenter evaluation of ED-based HIV screening programs using fourth-generation combination antigen-antibody HIV assays. This technology delivers a sensitivity and specificity of greater than 99% and provides significant advantage over third-generation platforms that test only for antibody.¹⁵ The ability to detect p24 antigen (present during acute HIV infection before the development of antibody), in addition to immunoglobulin M or immunoglobulin G antibodies (present after the immune response and diagnostic of established HIV infection), affords the opportunity to identify patients with either acute or established HIV infection.

During the approximate 3-year study period, 214,524 patients were screened for HIV infection in 9 urban EDs in major cities throughout the United States. All screening programs were conducted in locations with a relatively high prevalence of HIV infection and used non-risk-based (nontargeted) approaches to identifying patients for testing.^{16,17} Of the patients screened, 839 (0.4%) received a new diagnosis, and of these, 122 (15%; 95% confidence interval 12% to 17%) were identified with acute HIV infection. This study represents the largest cohort of acute HIV infections identified in EDs to date and provides a fairly generalizable understanding of the effect of combination antigen-antibody HIV screening on identification of patients with acute HIV infection in urban EDs.

Previous studies have reported proportions of acute HIV infections among individuals receiving a diagnosis of HIV infection, ranging from 0% to 43%.^{18,19} However, these estimates were driven by small sample sizes and single-site reporting, both of which limited their precision and generalizability. Also, before the introduction of combination antigen-antibody assays, the ability to efficiently identify patients with acute HIV infection required viral load testing or pooled nucleic acid testing, neither of which is routinely available in EDs or returns results in a timely manner.²⁰

The clinical relevance of diagnosing HIV infection during the acute stage, soon after initial infection, is of the utmost importance. Immediate treatment has been definitively shown to improve health outcomes^{21,22} and is particularly important because these individuals are particularly infectious until an antibody response has been established.²³ Moreover, the acute phase is the last time that symptoms from HIV may prompt patients to seek medical care for many years. The study by White et al convincingly demonstrates, for the first time, that a significant proportion of HIV infections detected in EDs are, in fact, acute cases, highlighting the importance of widespread ED adaptation of testing platforms capable of detecting such infections. However, the relatively nonspecific nature of the acute HIV syndrome (reinforced here by the authors' latent class analysis), together with the fact that acute infections are rare as a proportion of all HIV tests conducted (0.06% in this cohort), is a considerable challenge pointing to the need for further advancements in our understanding of the best approaches for screening in EDs.

The article by Leblanc et al¹⁴ was driven by previous research from that same group from 2012, which reported a large multicenter ED-based evaluation of nontargeted HIV screening

(without a comparison strategy) in 29 EDs in Paris.²⁴ They concluded that although nontargeted screening proved feasible, few new cases were diagnosed (0.1% of 12,754 patients tested), a finding that has been replicated by others.²⁵ They also observed that most patients identified with HIV infection belonged to “high risk” groups. These findings reopened the door to screening based on risk (targeted), and prompted the current study.

The current study describes a large pragmatic trial using a cluster randomized crossover design to evaluate nurse- driven targeted HIV screening combined with physician- driven diagnostic testing versus diagnostic testing alone, with the express purpose of evaluating the utility of targeted HIV screening in EDs. With verbal opt-out consent, adult patients without acute illness and with capacity to consent and complete a paper-based questionnaire were enrolled. The questionnaire was developed by consensus, with any affirmative response to 1 of the following 5 questions considered to indicate increased risk: any history of male to male sexual contact, greater than 5 sexual partners in the previous 12 months, sub-Saharan origin, sexual partner from a sub-Saharan country in the previous 10 years, or injection drug use. Nurses then offered testing to anyone who screened positive. Consenting patients underwent finger sticks to obtain blood for a third-generation antibody-only assay, from which results were available during the ED visit.

During the study’s intervention period, 31% of eligible patients (16,468) completed the questionnaire, and 26% (4,341) were identified as being at increased risk. Of patients at increased risk, 65% (2,818) completed testing, and 13 (0.5%) received a new diagnosis of HIV infection. Of patients with new diagnosis, all but one were men and either had male-to-male sexual contact or were of sub-Saharan origin. In comparison of the 2 arms, the intervention strategy (targeted screening and diagnostic testing) was slightly superior to the control strategy (diagnostic testing along), resulting in approximately 2 additional new HIV diagnoses per 10,000 patients tested. Despite the use of research staff to assist with clinical implementation, the pragmatic nurse-driven approach of this study provides further evidence of feasibility and a foundation to understand how targeted screening would practicably work in an ED, even if other targeted approaches varied in terms of selection criteria and testing yield.^{26,27}

Despite this considerable contribution, we are left with the same basic question of how best to select patients for HIV testing. Unfortunately, Leblanc et al¹⁴ did not compare targeted screening with nontargeted screening, and furthermore did not incorporate the additional factor of acute HIV detection. Recent findings of a large single center efficacy trial and a multicenter pragmatic trial of targeted versus nontargeted HIV screening in EDs showed no difference between strategies and exceedingly low rates of detection.^{27,28} This suggests that we have yet to identify an optimally sensitive and specific strategy for patient selection or to disentangle the results of a specific strategy from the results of imperfect implementation of that strategy.

The current and evolving landscape of HIV screening in EDs is clarified by these studies. In recent years, our specialty has primarily focused on strategies to expand implementation of nontargeted screening as recommended by public health authorities. The future must also now incorporate systematic and thoughtful approaches to identification of acute HIV

infections in EDs and further exploration of targeted patient selection strategies, both of which will become increasingly important to HIV prevention and the role of ED-based HIV screening as the prevalence of undiagnosed HIV infections continues to shrink nationally.

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