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HIV Screening of the Blood Supply in Developed and Developing Countries

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Abstract

In most developed countries of the world, the risk of human immunodeficiency virus (HIV) transmission by blood and blood products is extraordinarily small. This level of safety has been accomplished by successive refinements in donor screening and testing procedures. Various inactivation techniques have been successfully used in the manufacture of plasma derivatives and are being developed to inactivate bacterial and viral contaminants in cellular components. The most recent and powerful tool in this multi-layer safety net has been the introduction of nucleic acid techniques to capture donations from individuals in the very early stages of infection before a detectable serologic response has developed. This technique, while extremely costly, holds promise for other emerging agents that may pose a risk to the blood supply. In sharp contrast, in resource-poor countries of the world, blood transfusion remains a major avenue of transmission of HIV. Not only is much of the blood supply simply not tested, but there is a lack of infrastructure to support and equip blood banks, train personnel, recruit safe donors, promulgate the judicious and appropriate use of blood, and prevent anemia. A global collaborative effort is needed to ensure that there is a reliable and safe blood supply throughout the world.

Key words:

Blood transfusion. Transmission. Serology. PCR. NAT.

Introduction

In most developed countries of the world, extraordinary strides have been made over almost two decades to reduce the risk of human immunodeficiency virus (HIV) transmission by transfusion of blood and blood products. Prior to the discovery of HIV and the development of effective screening and testing measures to prevent its transmission, thousands of persons in the United States and worldwide became infected after receiving contaminated blood components or plasma derivatives. Cumulatively, nearly 9,000 cases of acquired immune deficiency syndrome (AIDS) due to receipt of unscreened blood and blood components had been reported in the United States through December 1999[1]. It has been estimated that half of the U.S. hemophilia population became infected with HIV before the development and incorporation of effective viral inactivation procedures in the manufacture of clotting factor concentrates[2]. In areas of the United States where the epidemic had a strong and early foothold, there has been a retrospective appreciation of the then significant risk of transfusion transmission of HIV. For example, in San Francisco it has been estimated that before the implementation of antibody screening, the risk of transfusion-associated HIV infection increased exponen-

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tially from 1978 through late1982, when it peaked at approximately 1.1% per transfused unit[3].

The successive introduction of donor history questions to screen for HIV-related high-risk behaviors, serologic testing of donations, and the development of effective sterilization and inactivation procedures for plasma derivatives have largely eliminated transfusion as a source of HIV infection in developed countries. Testing for HIV-1 p24 antigen and nucleic acid testing (NAT) of pools of donations have been implemented in many developed countries to further reduce the very small residual risk of HIV transmission attributable to donations from recently infected donors who have not yet developed detectable antibodies. Concomitant reductions in transfusion-associated hepatitis B and hepatitis C also have occurred with HIV blood screening strategies[4]. Finally, significant progress has been made in the development of promising thermal, chemical, irradiation, and fractionation techniques to inactivate contaminating viruses and bacteria in cellular components such as red blood cells and platelets[5,6].

In stark contrast, transmission of HIV and other infectious agents by blood transfusion remains a serious public health challenge in many developing countries. A variety of factors contribute to this situation, including the very high incidence and prevalence of HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) among blood donors; lack of organized and well-equipped blood banks; inadequate supply and distribution of serologic test kits, resulting in many donations not being tested at all; inadequately trained and supervised staff; reliance on paid or family replacement blood donors; cultural barriers to voluntary blood donation; inappropriate use of blood; and the high prevalence of chronic anemia in the general population[7]. Nonetheless, a few countries in sub-Saharan Africa have developed blood programs that have improved the safety and availability of blood[8-10].

This paper first will review current whole-blood donor screening and testing procedures for HIV in developed countries, with the United States serving as the case study. Similar practices would be expected to be in place in most other developed countries. The paper will conclude with an overview of the risk and prevention of HIV transmission by blood transfusion in the developing world.

Current HIV screening and testing procedures in the United States

Blood collection centers in the United States use a multi-pronged approach to minimize blood donation by persons at increased risk of infection with HIV and other bloodborne pathogens. However, the most significant measure to reduce the risk of transfusion transmission of bloodborne pathogens antedated the HIV epidemic in the United States. Concerns about the high rate of post-transfusion hepatitis led to the development of the National Blood Policy in 1973 and the move from paid donors to the establishment of an all-volunteer system of whole-blood donation[11]. This change, along with the implementation of serologic testing for hepatitis B surface antigen, was temporally associated with a marked decline in the incidence of viral hepatitis among transfusion recipients[12].

Donor education and screening

Although potential donors were queried about the use of injection drugs as part of an effort to minimize hepatitis transmission to transfusion recipients, education and screening of donors for behavioral risks and clinical signs were expanded once the basic tenants of the epidemiology and pathogenesis of HIV infections were elucidated. Since 1983, in an effort to reduce the likelihood that persons at increased risk for HIV infection would donate blood, the U.S. Food and Drug Administration (FDA) has required that all donors be given educational materials that describe the clinical signs and symptoms of HIV infection and AIDS and specific risk factors for acquisition of HIV infection[13-15]. In an effort to discourage persons from donating as a way to learn their HIV infection status, blood collection agencies also provide information about alternative sites where HIV testing can be obtained[14,15]. Additionally, donors are informed that blood collection agencies maintain and check registries of persons who have been found to be ineligible to donate blood. Further, blood collection agencies are obliged to follow local and state requirements for reporting of infectious diseases, should the donor test positive during the screening process[15].

In addition to having donors read informational brochures, the FDA recommends that blood collection staff privately ask each prospective donor direct oral questions about individual HIV risk behaviors[14,16]. Evaluation of this approach in the late 1980s and early 1990s demonstrated increased rates of HIV-related donor deferral when compared with the use of written screening information[17-20]. Finally, donors are required to sign a consent form which stipulates they understand that they should not donate blood if they are at risk of HIV infection and that, if their blood tests positive, they will be entered on a list of permanently deferred donors[14].

One novel, although questionably effective, measure to provide donors at increased risk of HIV infection a mechanism to prevent their donation from being used is the Confidential Unit Exclusion, or CUE, procedure[14,21]. The CUE option was developed because of concerns that individuals in certain settings (e.g., the workplace) might feel pressured to donate, despite knowing that they were at risk of HIV infection. Typically, after completion of the medical history questionnaire and interview, but before donation, individuals can choose one of two bar-coded peel-off labels to indicate if their blood should/should not be transfused to others. Systematic evaluation of the CUE option has found that although donors who indicated that their blood should not be transfused were significantly more likely to be HIV seropositive, the sensitivity of the procedure overall was poor, ranging from 2.3% in one study[22] to 3% to 5% in another[23]. Over time, the

use of CUE has declined. In November 1999, America's Blood Centers conducted a survey of 71 member centers and found that 42% of respondents did not use CUE; 42% used and planned to retain CUE; 13% used but planned to discontinue CUE; and 3% used a modified CUE procedure[24].

The donor history screening process is an important opportunity to interdict the donation and subsequent use of blood that may be infected with HIV or other bloodborne pathogens. Before the advent of HIV antibody testing of all donations in the United States in March 1983, several studies suggest that donor education and screening were very effective in reducing the risk of transfusion-associated AIDS[3,25,26]. For example, in the San Francisco Bay area, the implementation of high-risk donor education and exclusion measures was temporally associated with a significant decline in the risk of HIV infection per unit of blood; approximately 90% of high-risk donors (largely men who have sex with men) likely self-deferred or were deferred by the blood center before the initiation of HIV antibody screening of all donations[3].

Despite the documented successes of HIV-related donor education and screening, this approach has several well-recognized limitations. First, it requires that donors understand the informational material and/or the questions posed by the health interviewer; this need is especially challenging considering the range of educational, cultural, and language backgrounds of donors[27]. Second, donors must be willing to answer questions truthfully and self-defer when appropriate. Third, in some instances, donors may not be aware that they are at increased risk, such as persons who unknowingly have had sexual contact with persons who were infected with, or at risk for, HIV infection.

The Centers for Disease Control and Prevention (CDC), in collaboration with investigators from 15 blood collection centers, has interviewed HIV seropositive blood donors since 1988 to learn more about the epidemiologic, laboratory, and behavioral characteristics of this group[28]. Data from this study suggest that a large proportion of infected donors were aware of their risk at the time of donation (Table 1)[29]. Donors indicated various motivations for donation, including a desire to be HIV tested, peer pressure, receipt of a gift, or time off from work; additionally, the lack of privacy during the donation process was a concern for 80% and 88% of infected male and female donors, respectively[30]. Recently, Williams and investigators participating in the National Heart, Lung and Blood Institute-sponsored REDS (Retrovirus Epidemiology Donor Study) expanded the study of risk behaviors among donors to estimate the prevalence of undetected risk factors among persons who had donated blood successfully in the previous 2 months[31]. Using an anonymous mail survey, they found that 186 per 10,000 respondents (1.9%) reported an infectious disease deferrable risk (nearly all could be related to potential exposure to HIV) that was present at the time of their previous donation.

Recently, in the United States, there has been growing interest in evaluating the donor history screening process. Concern has been expressed about the number and complexity of questions that donors are asked, as well as their sensitivity in self-identification of high-risk donors. Re-examination of the donor history has been prompted in part by the development and implementation over the last couple of decades of extremely sensitive serologic and nucleic acid tests to detect infection with HBV, HCV, and HIV. FDA and the American Association of Blood Banks have embarked upon a series of workshops and formed a task force to revise the donor history questionnaire.

Screening and supplemental testing for antibodies to HIV-1 and HIV-2

In the United States, screening of all blood donations for antibody to HIV was implemented in March 1985. The most commonly used test format for serologic screening is the enzyme-linked immunosorbent assay (EIA or ELISA)[15,32]. Following the licensure of recombinant EIAs containing antigens for both HIV-1 and HIV-2, the FDA recommended that all donated blood, blood components, and source plasma be screened for antibody to HIV-2 as well as HIV-1[14,33].

Testing of donations for HIV follows a prescribed sequence (Fig. 1). Initially, a sample of serum or plasma is tested; if the sample is reactive, repeat testing is performed on both the original sample and an aliquot of plasma obtained from the segmented tubing attached to the blood component bag[32]. If one or both of these tests is reactive, the unit cannot be used for transfusion or further processing for manufacture of injectables. Further, all in-date components from prior donations by the individual are identified and quarantined, pending the results of further evaluation[14]. FDA recommends that supplemental testing be performed for all donations repeatedly reactive for anti-HIV-1/HIV-2 and prior to notification and counseling of individuals[14]. This testing is of particular importance in the blood donation setting, as the majority of reactive screening tests would be expected to be falsely positive, given the extraordinarily low incidence and prevalence of HIV infection among United States. blood donors.

Supplemental testing for HIV-1 should include an additional, more specific test. Most laboratories use a viral lysate-based Western blot, although an immunofluorescence assay (IFA) is also available for this purpose[15]. CDC and the Association of Public Health Laboratories (APHL) (formerly the Association of State and Territorial Public Health Laboratory Directors) have published recommended interpretive criteria for the Western blot assay[34] and 85% of laboratories routinely use these criteria[35]. According to these criteria, a test result is interpreted as positive only when any two of the following three bands are present: p24, gp41, and gp120/gp160. A negative test result requires the presence of no bands. Western blots with bands that do not meet the criteria for a positive blot are read as indeterminate. Persons with an indeterminate Western blot are counseled that they may be infected with HIV-1 and require follow-up testing at 1 month. After that

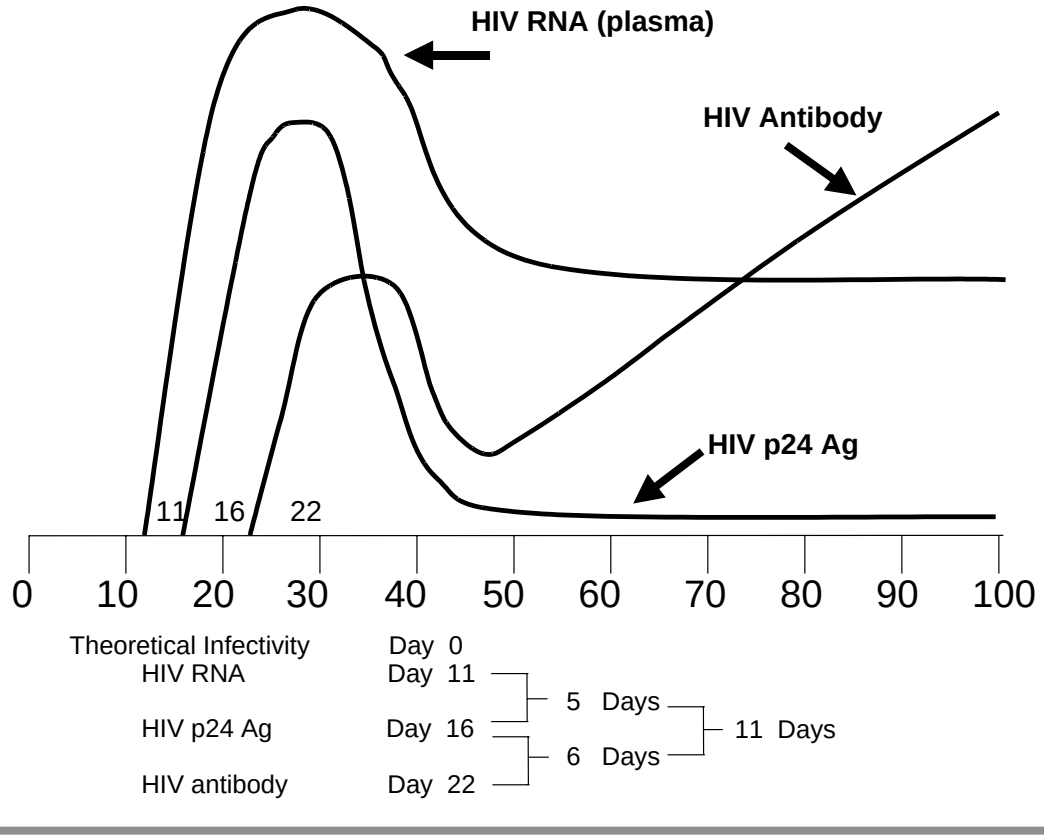

Fig. 1. *Decision tree for anti-HIV-1/HIV-2 testing of blood donors.**
**In addition, nucleic acid testing is performed in parallel on all donations using pooled testing algorithms. IFA=immunofluorescence assay; WB=Western blot. (Figure reprinted with permission from Fiebig W. Infectious Complications of Blood Transfusion. In: Vengelen-Tyler V, ed. Technical Manual. 13th ed. Bethesda, MD: American Association of Blood Banks, 1999:613.)*

time, persons with persistently indeterminate Western blot test results are considered to be negative for HIV-1, provided that they do not have any risk factors for HIV or clinical findings suggestive of infection[36]. However, the persistence of an indeterminate test result precludes these individuals from being blood donors[14].

Since publication of these interpretive criteria, long-term follow-up studies of blood donors with indeterminate Western blot results have been conducted. In these studies, donors were followed for subsequent clinical evidence of HIV infection and underwent further laboratory evaluation with polymerase chain reaction (PCR) and/or HIV-1 p24 antigen testing[37-39]. None of these donors had detectable HIV, suggesting that there is an extremely low rate of HIV infection among blood donors with indeterminate HIV-1 supplemental Western blot testing. False-positive Western blots (i.e., blot patterns meeting CDC/APHL criteria but showing no evidence of additional bands on follow-up testing and negative PCR test results) have been reported among blood donors[40]. Information derived from NAT (see below) should help to resolve these relatively infrequent events.

Supplemental testing for HIV-2 should be performed for persons with a repeatedly reactive combination test and whose HIV-1 Western blot or IFA result is negative or indeterminate, or for persons who may be at increased risk for exposure to HIV-2. This latter group includes persons born in or emigrating from sub-Saharan Africa and the nearby islands; sex partners of a person known to be infected with HIV-2 or from a country where HIV-2 is endemic; persons who received a transfusion of blood or a nonsterile injection in a country where HIV-2 is endemic; or children of women known to be infected with HIV-2 or have risk factors for HIV-2[14,33]. Individuals whose supplemental test result for HIV-2 is negative can be considered for reentry as a blood donor if they meet FDA-prescribed conditions for follow-up testing a minimum of 6 months after the initial sample is tested[14].

Epidemiologic and donor testing data indicate that the prevalence of HIV-2 among blood donors in the United States is very rare. Of more than 28.5 million donations screened by the American Red Cross during 1992 to 1996, only one was from a donor with confirmed HIV-2 infection[41]. Nonetheless, because of the potential for transmission by blood and blood products and the availability of licensed combination HIV-1/HIV-2 EIAs, the FDA recommended in June 1992 that blood donors be screened for antibodies to HIV-2[14,33]. No cases of transfusion-acquired HIV-2 infection have been reported in the United States, and only three HIV-2-in-

fected individuals have been detected among persons attempting to donate blood or plasma[41]. HIV-2 transmission by transfusion of blood and blood products has been reported in Europe[42].

Variant HIV strains among blood donors

To date, three groups of HIV-1 viruses have been identified: group M (major group); group O (outlier group); and most recently, group N. The number of group O infections reported worldwide is small and most have occurred among persons in West and Central African countries[43]. However, because HIV-1 group O is inconsistently detected by current EIAs for antibodies to HIV-1, concern has been raised about the potential implications for the safety of the blood supply in the United States[44]. Efforts are under way to encourage modification of existing HIV-1 EIAs to improve detection of group O strains without compromising sensitivity for the group M viruses. As an interim measure, FDA has recommended that donors at increased risk for HIV-1 group O infection because of residence or other ties to Central and West Africa be deferred from donation of blood[45]. To date, studies of blood donors in the United States have not found any evidence of infection with HIV-1 group O[46]. A recent epidemiologic and laboratory evaluation of persons identified through national HIV and AIDS surveillance data at increased risk for group O and group N infection because of their country of birth, found two persons infected with group O and none with group N virus[47].

Ten subtypes (A-J) of group M have been identified by using phylogenetic analysis of nucleotide sequences of the *env* region of HIV-1[43,48]. Most HIV-1 isolates in North America are subtype B, although a small number of United States-born persons have been found to be infected with non-B subtypes[48]. A recent study examined the prevalence and diversity of HIV-1 genetic subtypes among HIV-1-positive blood donors in the United States by using heteroduplex mobility analysis[49]. None of 97 donors retrospectively identified as being HIV-1 infected in 1985 and three (1%) of 383 donors prospectively identified between 1993 and 1996 were found to have non-B subtypes (2 subtype A and 1 subtype C). Two of the three donors were born in Africa; the third, however, was born in the United States and reported only heterosexual contact with American-born partners. Of note, this study did find an increase in *env* gene diversity among HIV-1 group B strains over time. A different pattern has been found among European blood donors. For example, researches in France found that the prevalence of non-B subtypes increased from 4% to more than 20% of potential donors who were found to be HIV-1 infected[50]. The emergence of non-B infections in the United States and other countries is of potential concern because blood donations are screened with antibody assays using subtype B synthetic peptides or recombinant-DNA-derived antigens which may not detect early infections with non-B subtypes during the period of seroconversion[51].

Table 1. *Reported risk behaviors of interviewed HIV seropositive blood donors, 1988-1998, The HIV Blood Donor Study, Centers for Disease Control and Prevention.*

	Risk Behavior (N = 1490)	Females,% (N = 637)
Male sexual contact	47	NA
Injection drug use	8	3
Heterosexual contact*	9	45
No risk identified	36	52

* Heterosexual contact with an injection drug user, man who has sex with men, or person with unclassified HIV infection or AIDS. See reference[29]

HIV-1 viral markers and evolution of laboratory testing methods

Recent studies of seroconversion panels from plasma donors, in combination with advanced statistical modeling techniques, have provided the most detailed picture of the dynamics of viremia during the early stages of HIV seroconversion[52-56]. These unique plasma panels included a large number of samples collected prior to and during the early period of rapid viral replication ("ramp-up" phase), permitting investigators to more clearly define the time course for detection and quantitative levels of viral markers (Fig. 2)[52-55]. Much interest has focused on developing a better understanding of when a person first becomes viremic following an infectious exposure (i.e., the length of the "eclipse" or pre-infectious phase) and the level of viremia associated with transmission by transfusion. Very recent work suggests that there is low-level (< 100g Eq/ml), intermittently detectable viremia prior to the ramp-up phase; studies to assess the infectivity of these viremic periods are being initiated[55].

Hand-in-hand with a clearer understanding of the events of early HIV infection has been the development and implementation of laboratory methods that permit rapid screening of large numbers of donations to accurately detect viral markers at increasingly earlier stages of infection.

Successive refinements of the serologic antibody assays have resulted in tests with extraordinary sensitivity and specificity. The earliest EIAs that were used to screen blood donations during 1985 through 1990 were based on a whole-virus lysate format and had an average window period of 45 days[57,58]. The average window period of the most sensitive contemporary recombinant protein-based EIAs for HIV-1 and HIV-2 is now estimated to be 22 days[58].

In March 1996, a new testing approach to further reduce the risk of transfusion-transmitted HIV-1 infection was implemented in the United States[57]. This approach was based on testing for a core structural protein of HIV-1 (p24 antigen), rather than an antibody response to the virus. HIV-1 p24 antigen detects HIV infection an average of 6 days before antibody tests are positive[58]. Initial projections

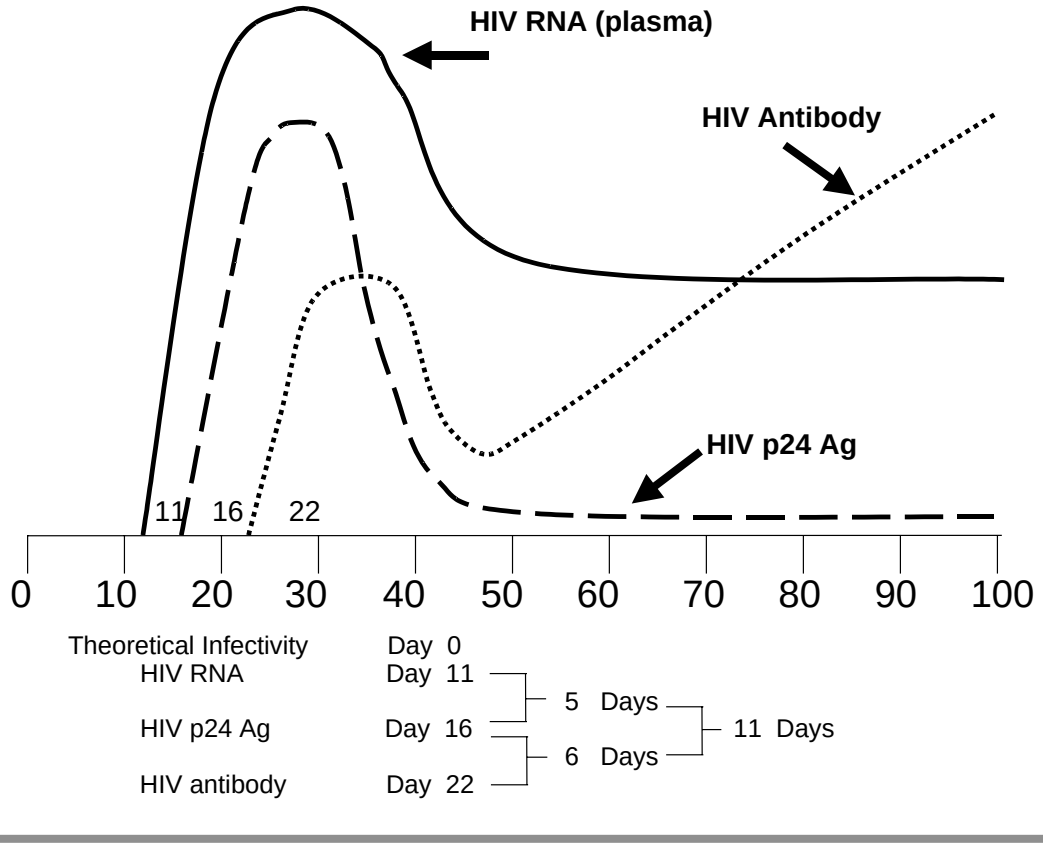

Fig. 2. *HIV markers during early infection.**
(Figure reprinted with permission from Transfusion 2000; 40, 143-59, published by the American Association of Blood Banks.

estimated that four to six infectious donations not captured by other screening tests (e.g., hepatitis B core antibody) would be detected among the 12 million blood donations collected annually[59]. However, since its implementation, only 10 antigen- positive/antibody-negative donations have been detected in the United States (range 1 in 4-6 million donations)[60,61]. It has been postulated that the yield of p24 antigen testing has been lower than anticipated because early estimates failed to take into account the likelihood that donors with acute HIV infection would either feel too ill to donate or self-defer because of engaging in recent high-risk behavior. Evaluation of inter-donation intervals for repeat whole blood donors has found longer-than-average intervals between donations around the time of HIV seroconversion[62,63]. Another troublesome aspect of p24 antigen testing has been an unexpectedly high number of false-positive results[63,64].

At the time the testing was implemented, FDA indicated that p24 antigen screening of donors would be an interim measure pending the availability of more advanced technology (e.g., NAT) to further reduce the window period[57,63]. The major impetus for the development and implementation of NAT of blood and plasma donations in the United States and other developed countries was the European Union requirement in 1999 that all plasma used in the manufacture of plasma derivatives sold in Europe had to be tested by NAT techniques for HCV and HIV-1 RNA[52].

Currently, virtually all whole-blood and plasma donations collected in the United States are being screened for both HCV and HIV-1 by NAT. This testing program has required the building of new and sophisticated laboratories and equipment, extensive training of personnel in molecular testing techniques, development of transportation systems to rapidly deliver approximately 50,000 donations per day to these laboratories for testing, and creation of complex data management systems for testing and reporting of results – all without disruption of the national blood supply and in a breathtakingly short period[53]. The testing, being done under FDA-approved investigational new drug applications, has posed some novel and challenging ethical and medico-legal issues[65]. Due to the complex and labor-intensive nature of the testing, it is being implemented using a pooled strategy – namely, donors are being tested in pools of 16-24 donations. At this relatively nascent stage, NAT can require several days more than conventional serologic tests. Consequently, certain components, particularly platelets because they outdate in 5 days, are being released by some blood centers before NAT has been completed and on the basis of serologic testing alone. As the technology evolves, it is expected that all components will be released on the basis of both NAT and serologic results.

Pooled NAT testing has been estimated to reduce the pre-HIV antibody seroconversion window period from the current 22 days to about 10-15 days (Table 2)[52,55]. Results from the first 14 months of NAT in the United States and Canada have found 4 NAT-positive/HIV-1 antibody-negative/HIV-1 p24 antigen-negative donations among 12.6 million donations screened, for an observed rate of 1 NAT-positive-only donation per 3,150,000 donations tested[60]. Although pooled NAT testing has resulted in an extremely low risk of HIV transmission by blood transfusion (see below), it has not eliminated rare cases of transmission due to the dilution of very low levels of virus in mini-pools[66]. Manufacturers have already begun development and testing of individual donor NAT testing systems[67,68]. Progression from minipool NAT to individual donor testing is estimated to yield extremely small gains in window period reduction for HIV (i.e., reduction in the window period by approximately 4 more days, yielding an estimated three additional infectious donations per year) and at extraordinarily high costs (i.e., 2.7 million dollars per case detected)[53,55].

Residual risk of HIV transmission

Transmission of HIV-1 by screened blood is now due almost exclusively to window period donations (i.e., donations from recently infected donors who have not developed detectable laboratory evidence of infection). Other potential ways that an HIV-infected unit of blood might enter the blood supply, such as laboratory testing errors, the failure of current tests to detect a variant of HIV-1, or persons with atypical seroconversion responses, are considered extremely rare (Table 2)[52,55].

Blood donors are a highly selected population and overall have far lower rates of HIV infection than the general population. Donor-based systems of surveillance, using data from the routine testing of blood donors, have demonstrated significant declines in the prevalence of HIV infection among donors[29,69]. For example, during the 10-year period from1988 through 1998, of more than 25 million donations tested, the overall HIV prevalence rate decreased from 0.023% to 0.005% ($p < 0.01$)[29]. In contrast, estimates of HIV prevalence in the general United States population are almost 100 times higher[70,71]. For example, trends in HIV prevalence among childbearing women in the United States from 1989 through 1994 ranged from 0.15% to 0.17%[70]. Use of a new approach (i.e., sensitive/less sensitive EIA) to identify persons in the period of early HIV infection when the antibody titer is rising but has not reached the peak level[72] showed that 19% of all positive donations during 1994 through 1997 were determined to be recent infections[29]. In this study, the highest rates of recent (incident) infection were more frequent among donors who were under age 35, white, from the southeastern region of the United States, and male donors who had sex with men.

With declining rates of HIV infection among blood donors and improved testing procedures, the likelihood of transfusion transmission of HIV has declined significantly. Risk estimates prior to NAT ranged from one case of HIV transmission for every 450,000 to 660,000 donations of screened blood in the United States (Table 2)[59,73]. Subsequent to the introduction of minipool NAT, the residual risk of HIV transmission is approximately one infection per million donations[55].

HIV transmission by blood transfusion in resource-restricted countries

Despite the extremely low risk of HIV transmission by blood transfusion in industrialized countries, increasing attention and resources are dedicated to increasingly expensive interventions with diminishing marginal benefits. In the first 18 months of p24 antigen testing in the United States, for example, approximately 18 million blood donations were tested at an estimated cost of U.S.$90 million to detect three antigen-positive-antibody-negative blood donations[64,74]. Blood safety in low-prevalence areas tends to have a high political profile and face high public scrutiny; health officials in many industrialized countries have faced criminal investigations regarding implementation of blood safety initiatives early in the AIDS epidemic.

Yet in many developing countries, where 90% of the world's HIV infections exist, the provision of a safe blood supply remains an important public health challenge. Fifteen years after development of commercially available HIV antibody screening tests, the World Health Organization (WHO) and others have estimated that 5%-10% of HIV infections worldwide are due to blood transfusion[8,75]. Inadequate resources for the procurement of test kits are rarely the sole limiting factor in securing a safe blood supply. Providing an adequate supply of blood that is collected from low-risk donors appropriately screened for infectious diseases in a controlled environment, and stored and distributed for appropriate clinical use requires a complex and often expensive health service delivery system. Such a system is difficult to attain in countries where resources, technology, and trained personnel are limited. Nonetheless, many resource-restricted countries have made important gains in the blood safety arena. This section summarizes research and program accomplishments in the area of international blood safety and the challenges that remain.

Establishing a national blood transfusion service

WHO has identified the establishment of a national blood transfusion service as a fundamental component of a blood safety program[76]. Securing a strong national commitment and developing a well-organized blood transfusion service serve as an advocacy tool for the development of needed oversight, authority, budget, and staff required to develop and implement a complicated and technically sophisticated health care service. That being said, obtaining a national commitment for an organizationally distinct blood transfusion service is often difficult to achieve. The development of a national

Table 2. *Estimated residual risk of HIV infection in the United States per 10 million blood donations by source of risk and screening test*

Test	Window Period	Viral Variants	Chronic Antibody-Negative Carriers	Testing Error	Total
EIA	24	< 0.6	0	0.4	25
MP-NAT*	16 - 32	0	0	0	13 - 14

EIA=enzyme linked immunosorbent assay; MP-NAT= mini-pool nucleic acid testing
* It is estimated that MP- NAT will shorten the HIV window period from 7 to 9 days (33%-41%) relative to that for HIV antibody testing. MP-NAT should detect most viral variants, testing errors, and all chronic HIV antibody-negative carriers.

policy and guidelines has helped to demonstrate a cohesive approach to blood safety and galvanize public support for transfusion services. These guidelines define a standard of patient care, increase the awareness of health care providers, and contain budget requirements for transfusion services[77].

Blood screening

Universal screening of the blood supply for HIV antibody remains the most fundamental element of programs to prevent HIV transmission by blood transfusion, yet many countries have not been able to achieve this most basic component of a blood safety program. Although many governments mandate screening of all blood transfusions, support for such programs by national governments and international aid organizations is often insufficient. Of 145 developing countries reporting to the WHO, 59% reported that all blood donations were screened for HIV antibody[78]. However, even in countries that reported 100% screening, supplies of test kits were sometimes interrupted[79]. In a study conducted in the Democratic Republic of the Congo (formerly Zaire), 28% of blood donations were not screened during the study period[80]. In Kenya, test kits were not available for 4 weeks of a 6-month study period[81]. WHO estimates that at least 13 million of the 75 million units collected in the world each year are not completely tested for transfusion-transmitted diseases.

Availability of test kits is an important factor, but only one component of a strong blood testing program. Testing technologies must be appropriate for different clinical settings. For example, many hospitals, particularly smaller hospitals or those serving more remote areas, often do not have functional blood banks with stored blood; patients' relatives may be requested to donate blood or even purchase blood bags and other supplies. In these types of generally low-volume settings, availability of rapid tests would be vital to decrease transfusion delays, decrease the cost of HIV screening, and improve availability of testing. HIV testing by various rapid testing algorithms has been shown to be essentially as sensitive and specific as algorithms using EIAs and Western blot (Fig. 3)[82-84]. Moreover, these often underutilized technologies could be implemented in countries where expensive, sophisticated equipment, a reliable power supply, and highly technical personnel may not be available.

Supervision and technical training

Attention to procurement and distribution of test kits alone, however, is not sufficient to ensure a safe blood supply. A key issue that is often overlooked in programs in developing countries programs is the need for technical training and supervision. In a survey of hospitals in central Africa, only 32% of the hospitals had standard practices for the recording of HIV test results[80]. Supervision of laboratory activities, quality assurance programs, and regulatory authority are often inadequate, or more often, nonexistent. In a multicenter study in Kenya, where test kits were provided to hospitals if they were otherwise not available, 30% of HIV-positive donations detected by screening were not removed from the blood supply. Many factors contributed to HIV risk, including poor record keeping, irregular labeling and storage of blood bags after screening, breaks in the cold chain during transport of test kits, collection of blood from relatives for immediate transfusion when rapid tests were not available, and the practice of one hospital to not screen mother-to-child transfusions because of the erroneous assumption that all mothers and infants have the same HIV infection status. These laboratory practices in a high-prevalence area resulted in the risk of HIV transmission by "screened" blood transfusions being 1 in 50 transfusions[81], approximately 10,000 times greater than that of the United States[59] and France[85]. On the basis of this evaluation, Kenya developed a national program to enhance laboratory training, improve record keeping, and ensure the distribution of rapid kits to small hospitals. Expanding local infrastructure to support blood bank management and oversight could have an important impact on the safety of the nation's blood supply.

Improving the appropriate use of blood

Blood transfusions are used frequently in many developing countries, owing mostly to the high burden of malaria-associated anemia among children and frequent complications of pregnancy, narrow child spacing, and nutritional deficiencies among women. Studies throughout sub-Saharan Africa, including the Democratic Republic of Congo, Kenya, Tanzania, and Côte d'Ivoire, have reported that 17%-26% of hospitalized children were transfused[86-89]. Children with severe anemia (hemoglobin < 5.0 g/dl) in western Kenya accounted for 30% of hospitalized

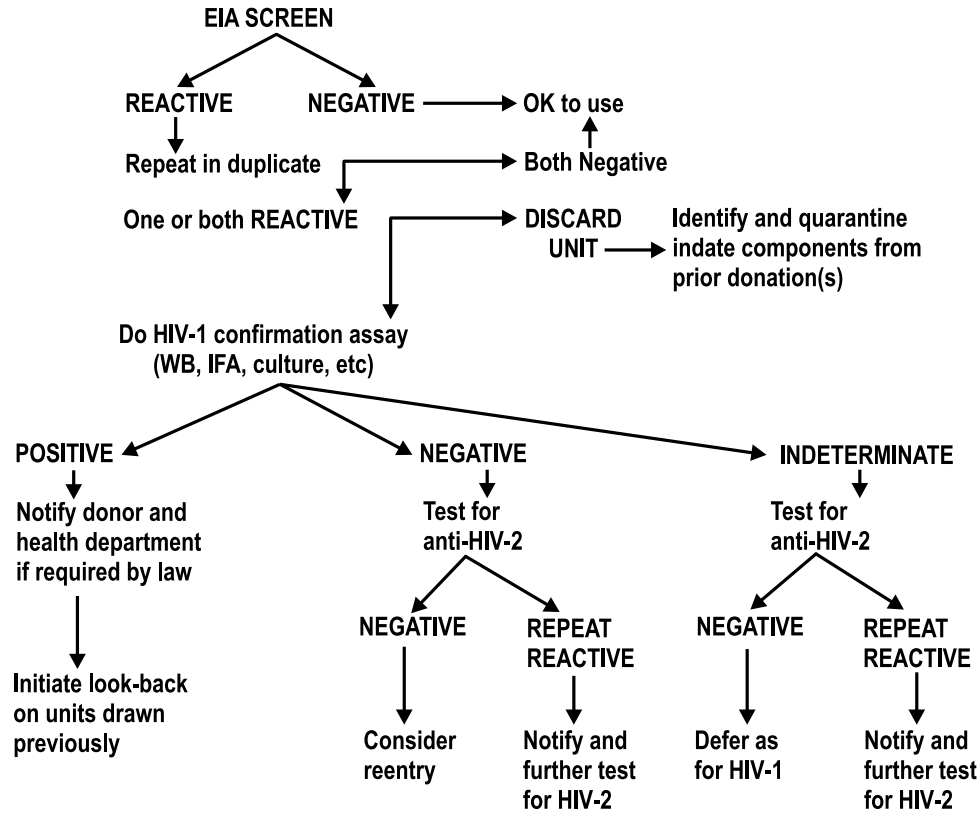

Fig. 3. *HIV screening algorithm in resource-poor setting*

children and 50% of in-hospital deaths[86]. In a household survey of Kenyan children, 20% of surveyed children had hemoglobin below 7.0 g/dl[90].

In many areas, such as Asia and Latin America, transfusions are used most frequently for treatment of surgical and trauma patients. In these settings, increased use of crystalloids (saline) and colloids as first-line treatment to increase intravascular volume has been emphasized as an important mechanism to reduce the unnecessary use of blood.

Despite the high prevalence of severe chronic anemia among women and children in Africa, many studies have demonstrated that the use of blood could be substantially reduced. National and local guidelines have been developed in numerous countries through literature review and consensus development. Studies conducted in the Democratic Republic of the Congo, Ghana, and Tanzania found that 13%-39% of transfusions could have been prevented had transfusion guidelines been followed[8,91-93]. A prospective study of severely anemic children was conducted in a malaria-endemic area of Kenya where shortages of blood were frequent. Children with hemoglobin levels below 4.7 g/dl and who also had clinical evidence of cardiorespiratory decompensation (intercostal retractions, flaring of the nares, or grunting) benefitted if transfused. In addition, in this area, which relied on family blood donations, more than 40% of transfusions were delayed 2 or more days while waiting for donors, supplies, or screening. Children who received transfusions 2 or more days after admission had the same probability of survival as those who survived at least 2 days but were not transfused[86]. Transfusions could have been reduced by more than 50% had they been limited to these clinical and temporal criteria. These studies also demonstrated that blood collected from family members cannot be administered to patients quickly, when they can have an improved chance of survival, and exposes patients to the risks of blood when they have little chance of benefit.

Donor recruitment and blood banking

These studies in transfusion practices underscore the fact that blood can be used appropriately and effectively only if it is collected, screened, stored, and available for immediate transfusion. However, because of financial and technical limitations, and because voluntary blood donation may not be readily understandable or acceptable in some cultures, many hospitals and blood banks rely on patients' friends or family members to provide or replace blood donations. Many areas still rely on paid donors. Family and paid donors, however, have been shown to be at increased risk for HIV infection compared with volunteer donors, and do not get blood to patients when they need it to improve survival[94-97]. Donor selection or deferral is

also difficult to implement when severe blood shortages exist and transfusions are urgently needed.

Many countries rely on hospitals to recruit their own blood donors and maintain their own blood banks. However, several problems exist with these decentralized systems. Expertise is lacking in most peripheral centers for effective donor education and mobilization, and sufficient resources are not allocated out of hospital budgets because of competing health priorities. Maintaining an adequate supply of blood collected from non-remunerated volunteer donors requires substantial resources for transportation, personnel, laboratory equipment, and refrigeration, and a reliable supply of consumables, such as blood bags and reagents. Numerous countries have advocated for the development of national or regional transfusion centers. Centralized blood banks improve standardization and oversight of services, enhance efficiency, and reduce costs through economies of scale. Centralized systems have been successfully implemented in some countries, including Zimbabwe, Rwanda, Uganda, and Côte d'Ivoire[8-10]. However, centralized systems are costly to implement and sustain and have often required substantial support from international donor agencies. With infrastructure problems, such as poor roads and communication systems, centralized systems often cannot adequately support the transfusion needs of remote areas or small hospitals. Alternative systems have been proposed in some areas, such as that in a remote area of the Democratic Republic of Congo, where training, supervision, and rapid tests were provided to remote district hospitals[98].

Prevention of severe anemia

Prevention of severe anemia cannot be overemphasized as a vital component to the prevention of anemia-associated mortality and transfusion-transmitted diseases. A number of countries in sub-Saharan Africa have reported that one-half to two-thirds of transfusions go to children for the treatment of malaria-associated anemia[89,91,97]. Continued use of chloroquine for the treatment of pediatric malaria in chloroquine-resistant areas has only exacerbated the problem of anemia and anemia-associated mortality[99,100]. Pregnancy-related complications, the second leading cause for transfusion, are often preventable and treatable in the context of routine antenatal care. Inexpensive methods to screen for anemia, such as the WHO Color Scale, should be considered an integral component of mother-child primary health care clinics in locations where anemia is prevalent. Increased attention to nutritional deficiencies, particularly among women and young children, expanded use of bed nets, and early detection and effective treatment of the causes of anemia in primary health care clinics would greatly reduce the extraordinary burden of anemia disease in resource-restricted countries.

Conclusion

The high level of safety in the blood supply of the United States and other developed countries is the result of nearly two decades of continued refinements and improvements in donor screening and testing. Much of this progress has been spearheaded by the devastating impact of the HIV epidemic on recipients of blood and blood products prior to effective preventive measures. NAT is the most recent (and costly) technologic advance to reduce the diminishing residual risk of transfusion-associated HIV infection. All of this improvement has served to heighten the disparity in transfusion risks from infectious diseases that faces much of the rest of the world. WHO has called on its member states and the international community to address the glaring inequality found in the area of blood safety, and to actively support this most preventable and cost-effective method of HIV prevention[101]. As part of this effort, Dr. Gro Harlem Brundtland, the Director-General of the WHO, made blood safety the theme of the April 7th, 2000 World Health Day to advocate for a reliable and safe blood supply for all. With attention to strengthening of comprehensive programs that focus on establishment of a national blood transfusion service, universal testing of all donations, laboratory and clinical training, regulation and oversight, improved use of blood, and prevention of anemia, the fundamental health need for safe blood can be made available throughout the world.

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