Residual risk of transmission of HIV through blood transfusion in South Africa

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Abstract Despite the ongoing review of donor recruitment criteria by local blood transfusion services and the development of highly sensitive and specific testing for the presence of antibodies to HIV in blood and blood products, there remains a residue of HIV in donated blood. This is because of donors who are in the 'window period' between acquisition of HIV and seroconversion, human errors and limits to the sensitivity and specificity of current tests. Data available from a national survey of HIV seroprevalence in South African blood donors allowed for the estimation of the number of units screened negative but likely to be infected with HIV. Assuming window periods of 4,8 and 14 weeks, a test sensitivity of 99,9%, a specificity of 98,5% and a human error rate of 0,1%, the likely rate of HIV-infected blood in the South African blood transfusion supply ranges from 1,1 to 3,9/100 000 units, with a likely estimate of 2,2/100 000 units. In the current South African blood transfusion setting, between 8,1 and 28,2 units of blood per annum will be HIV-positive with a likely estimate of 15,9 units. This corresponds to an odds ratio of between 1:90 909 and 1:25 641 units infected with HIV. These data are comparable with the risk in developed countries. The expected increase in the incidence and prevalence of HIV infection in all adult South African populations necessitates additional measures to ensure a blood supply which is as safe as possible. Some of these measures have already been taken by local blood transfusion services.

In countries with well-developed policies on blood transfusion, including South Africa, the risk of transmission of HIV to recipients is now nearing the minimum that is technically possible. This has been achieved since 1985 through, for example, the exclusion of blood donors whose behaviour may put them at risk of HIV infection, the application of highly sensitive and specific tests to screen all donated blood for antibodies to HIV, and virus inactivation of blood products. There remains, however, a residue of infections because of infected blood donors who are in the 'window period' between acquisition of HIV and seroconversion, human errors and the limits to the sensitivity and specificity of the antibody test. The risk of seroconversion after trans-

fusion of HIV-infected blood has been shown to be 44/46 (96%) in Zaire.[1] Experience in both the USA and Zambia has shown that AIDS may develop rapidly after infection by transfusion, related possibly to the size of viral inoculation.[2,3]

There have been four distinct approaches to calculating the residual risk of transmission of HIV by blood transfusion. An epidemiological approach assumed that all HIV infections detected serologically in first-time donors were pre-existing or prevalent infections, and that all infections detected in repeat blood donors were new or incident infections. During 1986 - 1987, 0,012% of repeat blood donors and 0,041% of first-time blood donors in the USA had HIV antibody. Ward et al.[4] assumed that the median length of the window period was 8 weeks and calculated the rate of HIV infections by HIV-antibody-negative blood donations to be 2,6/100 000. The estimated rate of HIV-infected units entering the supply from American Red Cross donations in 1987 was 0,65/100 000, and the rate was falling by more than 30% per year.[5]

A second approach has been to measure the incidence of HIV in defined populations of patients who have high requirements for blood transfusions. Two seroconversions were observed after 80 630 units of blood or blood components were transfused to patients undergoing cardiac surgery in Baltimore and Houston; this gave an estimated risk of HIV-infected units of 2,5/100 000 with an upper 95% confidence limit of 7,8/100 000 units.[6,7] The observed incidence of HIV since the introduction of antibody screening in a transfusion-dependent population of Italians with thalassaemia major showed that the residual risk of HIV-infected units was approximately 2/100 000 units.[8]

A third approach, a retrospective 'lookback' method, consisted of HIV antibody testing of living recipients of HIV-seronegative units donated by persons who later tested HIV seropositive at the time of a subsequent donation. In Los Angeles it was estimated that the residual risk of HIV-infected units was most probably 1,47/100 000, and was within the range 0,99 - 1,98/100 000 units;[9] these calculations were based on observations from repeat donors, and may be underestimates if the incidence of infections is higher in first-time than in repeat donors.

A fourth approach measured the prevalence of HIV in 71 800 HIV-seronegative donations through the detection of virus by culture and polymerase chain reaction. In California, the probability of an HIV-seronegative donor being infected was estimated to be 1,6/100 000 units, with an upper 95% confidence limit of 9,4/100 000 units.[10]

All four approaches have yielded results which are remarkably consistent and suggest that in north America and western Europe the residual risk of HIV-infected units is most probably in the range of 0,65 - 2,6/100 000 units.

The risks are significantly greater when blood donors test anti-HIV-negative in tropical Africa. In the Ivory Coast in 1991 the overall prevalence of HIV was 11,0% in first-time blood donors and 2,1% in repeat blood donors. The incidence of HIV infection in first-time and repeat blood donors was assumed to be the same, 1,2% per year. However the authors unnecessarily multiplied the risk of infection in the repeat donors by the fre-

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quency of donations. This is incorrect and overestimates the residual risk of HIV infection of blood products in the repeat donor population. The risk of a unit being infected with HIV is unrelated to the frequency of donations (see 'Methods'). After the necessary correction, we calculate the risk of HIV infection from blood transfusion in the Ivory Coast to be 2,4 - 4,4/1 000, compared with the authors' calculated 5,4 - 10,1/1 000 units.[11]

Recent data available from a national survey of HIV seroprevalence in South African blood donors[12] allowed for the estimation of the overall number of units screened negative but likely to be infected with HIV.

Methods

The following need to be taken into account in the estimation of blood units likely to be infected with HIV despite screening:

1. **The accuracy of the screening test.** This entails the false-negative value of a test (FN), defined as the proportion of blood samples falsely showing a negative result, but which are, in fact, HIV infected, or 1 minus the predictive negative value of a test. The FN is dependent on the sensitivity (S, assumed to be 99,9%), the specificity of the test (Q, assumed to be 98,5%) and the prevalence (P) of HIV infection among the donor population.[13]

$$FN = 1 \frac{(1-P) \times Q}{(1-S) \times P + (1-P) \times Q}$$

Number of units per 100 000 missed by the test = FN × 100 000.

Given the current 0,2% approximate prevalence rate of HIV infection in the South African blood transfusion setting, the number of false negatives would be 0,2/100 000 units and is therefore ignored. These sensitivities and specificities are, however, calculated against a Western blot assessment which may fail to identify the presence of some recent HIV infections.

2. **Window period** (WP). The time between infection with HIV and a positive antibody test is the most important cause for concern in blood transfusion settings. Estimates of the window period range from 4 to 14 weeks with a most likely period of 8 weeks.[4-6]

3. **Human error** (HE). This is unlikely given the competence of blood transfusion technical staff. Nevertheless, an error rate of 0,1% (or 100/100 000) was assumed as a worst-case scenario, as was done elsewhere.[4]

4. **Incidence and prevalence assumptions.** In first-time donors the given prevalence of HIV infection was 0,198% (198,065/100 000).[12] To calculate the incidence of infection (I), data are required on the duration (D) of HIV infection (I = P/D). In the absence of such information for South Africa and for the sake of simplicity the duration was assumed to be 5 years.[4]

For *first-time* donors, the formula for calculating the proportion of units likely to be positive but undetected by screening is I × WP/52 + (P × HE).

For *repeat* donors both the incidence rate and the window period have to be adjusted for the interval between donations. Therefore if F is the frequency of donations per year, the formula becomes: (Annual incidence rate/F) × (WP/52) × F + (HE × P). This reduces to: I × WP/52 + (HE × P).

In other words, unlike the assumptions of Savarit *et al.*[11] the risk of units being infected with HIV is unaffected by the number of donations per year. In the repeat donor population the prevalence of HIV infection is calculated by multiplying the annual incidence rate by the period between screens (D_s). In the repeat donors the measure of prevalence (i.e. the overall number of positive results at one time) becomes equivalent to the

incidence rate (the number of new occurrences on each interval between donations).[5]

Results

For *first-time* donors, assuming a window period of 4 - 14 weeks, with a most likely period of 8 weeks, the risk of undetected units infected with HIV ranges between:

Minimum = 39,6 × (4/52) + (198,065 × 0,001) = 3,2/100 000 units;
Likely = 39,6 × (8/52) + (198,065 × 0,001) = 6,2/100 000 units;
Maximum = 39,6 × (14/52) + (198,065 × 0,001) = 10,9/100 000 units.

The incidence in South African *repeat* donors over a 6-month period ranged from 0,0006% to 0,006%,[12] the midpoint of which is 6,6/100 000 per annum. The average frequency of donations per year was 2,7 (R. L. Crookes — personal communication). This translates as a donation every 12/2,7 = 4,44 months (D_s = 0,37 years). The incidence of HIV per screening interval in repeat donors is therefore 6,6 × (4,44/12) = 2,46/100 000 (per 4,44 months). The prevalence of HIV infected units in repeat donors is I × D_s = 6,6 × 0,37 = 2,46/100 000. The risk of units being infected with HIV but undetected by screening given window periods of 4, 8 and 14 weeks would then be:

Minimum = 6,6 × (4/52) + (2,46 × 0,001) = 0,5/100 000 units;
Likely = 6,6 × (8/52) + (2,46 × 0,001) = 1,0/100 000 units;
Maximum = 6,6 × (14/52) + (2,46 × 0,001) = 1,8/100 000 units.

Roughly 810 000 donations are made each year, 185 000 of which are from first-time donors and 625 000 from repeat donors.[12] Assuming 90% are used to make red blood cell, plasma and other non-heat-treated blood components, 562 500 units from repeat donors and 166 500 units from first-time donors are potentially at risk.

The total number of undetected HIV-infected units per annum for first-time donors therefore ranges from a minimum = 166 500 × (3,2/100 000) = 5,3 units, to a maximum = 166 500 × (10,9/100 000) = 18,1 units, with the most likely estimate 166 500 × (6,2/100 000) = 10,3 units.

For repeat donors the number ranges from a minimum = 562 500 × (0,5/100 000) = 2,8 units, to a maximum = (562 500 × (1,8/100 000) = 10,1 units, with the most likely estimate 562 500 × (1/100 000) = 5,6 units.

In any 1 year, therefore, between 8,1 (5,3 + 2,8) and 28,2 (18,1 + 10,1) units of blood will be HIV-positive and undetected by screening with 15,9 units the most likely estimate. This translates as an odds ratio of 1:90 909 to 1:25 641 units being infected with HIV (likely = 1:45 849). In other words, the risk of HIV infection per 100 000 units ranges from 1,1 to 3,9, with a most likely estimate of 2,2 units.

In the USA, an average of 5,4 units are required per transfusion.[4] By contrast, in the South African Blood Transfusion Services (SABTS), 2,3 units are required per case (A. Du P. Heyns — personal communication). Assuming that the SABTS data of 2,3 units per case reflect a nation-wide average, this would translate in South Africa as an odds of 1:39 526 to 1:11 148 persons accidentally acquiring HIV-infected blood from blood transfusion (likely: 1:19 934), or a risk of 2,53 - 9,0/100 000 persons. These risks decrease to a more favourable level if due adjustments are made for the mortality rates of the conditions requiring blood transfusion. These data are, however, not available for South Africa.

Discussion

The estimated risk of residual HIV infectivity of transfused blood in South Africa is in the same range as that estimated in the USA and Italy.[4-10] The slightly higher risk in South Africa when compared with some of the data from the USA is a reflection of the higher prevalence in first-time donors and higher incidence of infection in repeat donors.

In South Africa, between 1986 and 1991, 73% of blood donors were white and 15% black.[12] The seroprevalence of the adult black population is currently doubling approximately every year and it is predicted that by the year 2005 between 18% and 24% of the adult population will be infected with HIV-1.[14-16] At the present stage of the pandemic, heterosexual transmission of HIV is affecting the black population worst, but it is foreseen that there will be a rising incidence and prevalence in the whole heterosexual community of South Africa. The inevitable increase in seroprevalence of HIV will lead to an escalating danger of HIV being transmitted by the transfusion of blood which tests antibody negative. Black donors happen to have the highest prevalence of HIV at this stage of the epidemic, but in all other respects the full participation of the black population in the voluntary blood donation scheme is both desirable and likely to happen, especially after political enfranchisement. A closer coincidence between the donor population and the recipients of blood results in (i) the more economical use of blood, e.g. there would be no excess of group A blood drawn from white donors and not utilised; (ii) a greater ease in finding compatible blood, e.g. a sufficient supply of group B; and (iii) a reduced risk of allo-immunisation.

It is important to emphasise that high- or low-risk behaviour is not restricted to one population group and exclusion of blood donors on the basis of their population group alone would be unacceptable. Some blood transfusion services are pursuing a policy of recruiting lower-risk black blood donors who, for example, include men between 16 and 20 years and people of both sexes over the age of 45 years.[17] Important risk factors associated with the transmission of HIV include multiple sex partners, lower rates of condom use and the presence of sexually transmitted diseases.

It should be a priority continually to revise national policy to limit the transmission of HIV through blood transfusion. Strategies which could be considered include: (i) an intensive campaign of education among potential blood donors as to the importance of heterosexual transmission of HIV and the undesirability of donors who have multiple or unknown sex partners; (ii) pre-donation education should be targeted at teenagers, because the recruitment of young adults as first-time donors is essential for the maintenance of the blood supply, and they are the age group most likely to be in the window period; (iii) the expansion of the pool of regular donors who repeatedly test HIV negative; (iv) the recognition of groups with a high frequency of HIV risk behaviour which, in the African context, include sex workers, prisoners, inhabitants of single-sex hostels, the uniformed services and long-distance lorry drivers;[18,19] (v) the use of blood from first-time blood donors for the preparation of virus-inactivated blood components and laboratory reagents only; (vi) a constant search for and the application of new tests of greater sensitivity, capable of detecting HIV during the window period; (vii) the preparation, dissemination and application of national guidelines on the appropriate use of blood and blood products, based on those of the Global Blood Safety Initiative of the Global Programme on AIDS of the World Health Organisation;[20] and (viii) primary health care interventions aimed at reducing the frequency of the need to transfuse through, for example, the prevention of anaemia in childhood and pregnancy and the anticipation of obstetric haemorrhage and other complications.[18,21]

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