Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology
8:506–510 © 1995 Raven Press, Ltd., New York

Rates of Mother-to-Child Transmission of HIV-1 in Africa, America, and Europe: Results from 13 Perinatal Studies

The Working Group on Mother-To-Child Transmission of HIV

Summary: The goal of this exercise was to provide estimates of the mother-to-child transmission rate (TR) of human immunodeficiency virus type 1 (HIV-1), calculated according to standardized methods. Prospective cohort studies in Africa (8), the Caribbean (1), Europe (3), and the U.S.A. (1) observed from birth children born to women known to be HIV infected at the time of delivery. TRs were calculated and compared by investigators during a meeting in Ghent (Belgium) in September 1993 according to agreed methodology. TRs were calculated following the direct and the indirect methods developed in 1992 by the Ghent Working Group. The direct method uses a classification of children born to HIV-seropositive mothers according to their probable HIV infection status at 15 months of age or before, if they die or are lost to follow-up. Minimum, intermediate, and maximum estimates of TR are computed depending on how children classified as indeterminate are counted. The indirect method is applied for studies with a comparison cohort of children born to HIV-seronegative mothers. TRs in developed countries ranged from 14 to 25% with the direct method (intermediate estimate). In the developing world, they ranged from 13 to 42% with the direct method, from 21 to 43% with the indirect method, and most of the studies reported a TR in the range of 25 to 30%. With use of a standardized methodology, the overall TR of HIV-1 tends to be higher in Africa than in Europe or the U.S.A. The variation in TRs is probably due to differences in factors associated with increased risk of transmission. This is of importance for the design and implementation of trials evaluating interventions aimed at reducing mother-to-child transmission of HIV. Key Words: HIV–Children—Mother-to-child transmission—Methodology.

Published estimates of the mother-to-child transmission rate (TR) of human immunodeficiency virus type 1 (HIV-1), based on information from prospective cohort studies, range from 13 to 48% (1). It is unclear how much of this variation can be explained by methodological differences between studies, such as the definition of infection, length of follow-up, high mortality of children of indeterminate infection status, and loss to follow-up (1,2). These methodological differences hinder comparison of the TR estimates reported by various studies. This paper provides estimates and compares TRs calculated according to two standard methods developed by the Ghent Working Group in 1992 (1), with use of information provided by investigators from 13 prospective cohort studies during a meeting held in Ghent (Belgium), September 3–5, 1993.

Address correspondence and reprint requests to Pr. François Dabis at INSERM U. 330, Université de Bordeaux II, 146 rue Léo-Saignat, 33076, Bordeaux Cedex, France.

Manuscript received March 28, 1994; accepted November 9,1994.

METHODS

A classification system of children born to HIV-1–infected mothers according to their probable HIV infection status during

the first 15 months of life has been proposed for estimating TR (1). Children are considered to be infected if HIV antibody persists beyond 15 months, if they die of an HIV-related cause, or if acquired immunodeficiency syndrome (AIDS) has been diagnosed. Children are considered to be uninfected if they are antibody negative at 15 months, or, in a child who was seronegative at 9 months or older and who subsequently was lost to follow-up or died of a non–HIV-related cause, antibody has disappeared at 9 months of age or after. Indeterminate HIV infection status is defined as a death or loss to follow-up before 15 months of age in the absence of AIDS in children still antibody positive (but in whom this could reflect maternal antibody).

The direct method of calculation of TR applies the classification previously described to cohorts of children born to HIV-seropositive mothers with sufficient follow-up. The minimum estimate of TR assumes that all children with an indeterminate infection status are uninfected. The intermediate estimate excludes indeterminates from the calculation, assuming that their proportion of infection will be the same as in those children with known infection status. The maximum estimate assumes that all children with an indeterminate infection status are infected. The standard error of TRs obtained with the direct method is calculated with the standard method for proportions (1). This direct method was applied to 12 data sets from Africa (3–9), the Caribbean (10), North America (11), and Europe (12–14).

The indirect method of calculation of TR uses persistence of antibody at 15 months of age in the cohort of children born to HIV-seropositive mothers together with an estimate of HIV-associated mortality (1). An estimate of excess, HIV-related mortality is obtained by comparing during the same follow-up period mortality of children born to HIV-seropositive mothers with that of infants born to HIV-seronegative mothers (comparison group). All of the excess infant deaths are assumed to be due to HIV-1 infection (10). The probability of dying before 15 months is estimated with use of survival analysis techniques, regarding loss to follow-up as a censoring event. A method of calculation of the variance of TR using the indirect method has been developed (1). Seven teams, six from Africa (3,5,7–9,15) and one from Haiti (10), had a comparison cohort and were therefore able to compute a TR with the indirect method.

RESULTS

Table 1 shows the TRs obtained with the direct method. The intermediate estimates range between 12.7 and 42.1%. The minimum estimates range between 10.0 and 33.9%, and the maximum estimates between 25.0 and 61.9%. The three European studies reported results for a total of 2,271 children born to HIV-seropositive mothers and observed prospectively from birth (12–14). Of these, 342 (15.1%) were classified as HIV infected, 1,638 (72.1%) as uninfected, and 291 (12.8%) as having an indeterminate HIV infection status. The difference between the rates obtained from the three European studies is statistically significant ($p = 0.002$). Seven African studies observed a total of 1,725 children born to HIV-seropositive mothers (3–9): 390 (22.6%) were classified as HIV infected, 961 as uninfected (55.7%) and 374 (21.7%) remained with an indeterminate HIV infection status. The rates from these seven studies differ significantly ($p < 10^{-6}$).

Estimates of TR obtained with the indirect method ranged from 20.7 to 42.8% (Table 2). In five of the six developing country studies for which both direct and indirect estimates were available (3,5,7–9), there was close agreement between the intermediate estimate of the direct method and the indirect method estimate (Fig. 1).

DISCUSSION

The results of this exercise show clearly that the overall rate of vertical transmission of HIV-1, in-

TABLE 1. *Range of estimates of the mother-to-child transmission rate (%) of human immunodeficiency virus type 1 (HIV-1) using the direct method of calculation proposed by the Working Group on Mother-to-Child Transmission of HIV-1 (Ghent, Belgium, September 1993)*

Location of the study (reference)	No. of children enrolled	No. of children with indeterminate HIV infection	Minimum estimate (SE)	Intermediate estimate (SE) £	Maximum estimate (SE)
Congo (3)	118	19	33.9 (4.4)	40.4 (4.9)	50.0 (4.6)
Côte d'Ivoire (4)	101	12	21.8 (4.4)	24.7 (4.6)	33.7 (4.7)
Kenya (5)	365	125	27.7 (2.3)	42.1 (3.2)	61.9 (2.5)
Rwanda (Butare) (6)	198	36	16.2 (2.6)	19.8 (3.1)	34.3 (3.4)
Rwanda (Kigali) (7)	218	32	21.1 (2.8)	24.7 (3.2)	35.8 (3.2)
Uganda (8)	402	92	18.7 (1.9)	24.2 (2.4)	41.5 (2.5)
Zaire (9)	323	58	22.9 (2.3)	27.9 (2.9)	40.9 (2.7)
Haiti (10)	480	267	10.0 (1.8)	12.7 (2.3)	28.2 (2.7)
New York City (11)	245	64	18.4 (2.5)	24.9 (3.2)	44.5 (3.2)
European Collaborative Study (12)	1,025	130	12.3 (1.0)	14.1 (1.2)	25.0 (1.3)
France (13)	946	101	18.2 (1.2)	20.4 (1.4)	28.9 (1.5)
Switzerland (14)	300	60	14.7 (2.0)	18.3 (2.5)	34.7 (2.7)

SE, standard error; £, best estimate of TR with the direct method according to the investigators. For Haiti, the estimate obtained with the indirect method (see Table 2) is considered more appropriate.

TABLE 2. *Estimates of the mother-to-child transmission rate of human immunodeficiency virus type 1 (HIV-1) using the indirect method of calculation proposed by the Working Group on Mother-to-Child Transmission of HIV-1 (Ghent, Belgium, September 1993)*

Location of the study (reference)	Estimate of the transmission rate (SE)
Congo (3)	42.0 (5.0)
Kenya (5)	42.8 (3.0)
Malawi (15)	35.7 (2.4)
Rwanda (Kigali) (7)	25.7 (3.5)
Uganda (8)	26.5 (2.5)
Zaire (9)	25.4 (3.2)
Haiti (10)	20.7 (2.6)

SE, standard error.

cluding postnatal transmission, is higher in Africa than in Europe.

The rates calculated with use of the direct method should be interpreted cautiously. Slightly different definitions for HIV-related deaths and HIV-related signs and symptoms have been used between study groups despite efforts of standardization (1). The intermediate estimate, which is the most often used, has a limited precision as children with an indeterminate HIV infection status are excluded from the calculation. Furthermore, this intermediate estimate assumes that the children classified as indeterminate were infected in the same proportion as children whose HIV status is confirmed. The effect of any bias on such estimates will depend on the size and age of loss to follow-up or death and on differences in inclusion and exclusion criteria in cohorts. For example, the maximum estimate in the European Collaborative Study is due to a relatively high loss to follow-up in the first few months of life. It is unlikely that all these children are infected (12). In other studies, failure to return for the early follow-up visits is a reason for exclusion from the cohort and would then not feature in the calculation. Similarly, it is unlikely, in any setting, that all children with indeterminate infection status are infected, rendering all maximum estimates unrealistically high. Indeed, experience in several settings would suggest they are likely to be uninfected.

In the Haiti perinatal study, blood for HIV antibody testing was available from only half of the infants born to HIV-infected mothers during the first year of follow-up (10). There were large numbers of infant deaths for which the investigators were unable to determine cause of death and HIV infection status. It is most unlikely that all these children were uninfected, making the minimum and even intermediate estimates of TR likely to be underestimates.

In the Kenyan study, children were classified as infected if they were antibody positive at any age beyond 15 months. Many children of this cohort, unique among the 13 studies included in this report, were evaluated as transient seroreverters or late seroconverters, i.e., becoming antibody positive after having been antibody negative, and have been classified as infected (5). This phenomenon might help explain the unusually high TRs reported in this case. It has been suggested by the study investigators that breast-feeding transmission could be responsible for this high frequency of late seroconversion (5). However, in other studies, late transmission through breastfeeding appears restricted to exceptional circumstances (16), and further investigations are required to clarify this important observation.

The indirect method of calculation of TR is less influenced by survival and ascertainment biases than the direct method because survival analysis, such as the Kaplan-Meier technique (17), allows for loss to follow-up. However, the assumption that all excess mortality in the cohort of children born to HIV-infected mothers compared with mortality of children born to uninfected mothers is due to HIV infection is also subject to bias. Some of this excess mortality could in fact be due to the indirect effects of the maternal illness and possible death of an uninfected infant living in difficult conditions, e.g., orphan or child receiving poor nutritional support from a sick mother. Indeed, children born to HIV-infected mothers have been shown to have higher mortality rates, irrespective of their own HIV infection status (18).

TRs calculated with the indirect method were similar to the intermediate estimates obtained with the direct method for all studies but the Haiti study, which chose to report the TR obtained by the indirect method for the reason explained above. These results suggest that, despite differences in the two approaches, both direct and indirect methods provide reliable estimates of the overall rate of vertical transmission of HIV-1 and that they can be used for the purpose of comparisons.

CONCLUSION

In summary, the TRs observed in developed countries ranged from 14 to 25%. In the developing world, most of the studies reported an overall rate

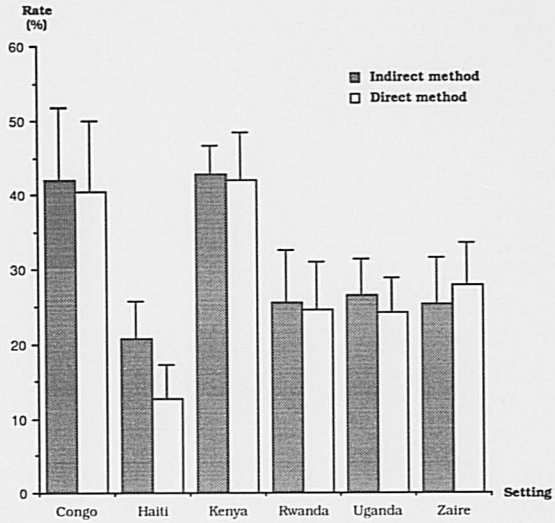

FIG. 1. Estimates of the mother-to-child transmission rate (95% confidence intervals) of human immunodeficiency virus type 1 (HIV-1) in six developing country studies (3,5,7–10) using the direct method of calculation (intermediate estimate) and the indirect method proposed by the Working Group on Mother-to-Child Transmission of HIV-1 (Ghent, Belgium, September 1993).

of transmission in the range of 25 to 30%, regardless of the method of calculation. Thus, the risk of mother-to-child transmission of HIV-1 tends to be higher in children born to HIV-seropositive mothers in Africa than in Europe. It is unlikely that there is a single explanation to account for this variation, and determinants of transmission are likely to differ between populations (19). Although individual studies have investigated risk factors for vertical transmission (20), it may be of interest to compare risk factor distributions of the various study populations. Such factors to be studied include obstetrical procedures, chorioamnionitis, maternal viral load, maternal viral characteristics, syphilis, and malaria. Knowledge of such determinants and acknowledgment of the difference in TRs between populations is of importance for the design and implementation of trials evaluating interventions aimed at reducing mother-to-child transmission of HIV-1, especially if a multicenter design is considered (21).

APPENDIX

The 1993 Working Group on Mother-To-Child Transmission of HIV consisted of the following persons. Scientific Secretariat: François Dabis (France), Lieve Fransen (EEC AIDS Task Force), Neal Halsey (U.S.A.), Philippe Lepage (Belgium), Philippe Msellati (Côte d'Ivoire), Marie-Louise Newell (United Kingdom), Benjamin Nkowane (World Health Organization Global Programme on AIDS), Catherine Peckham (United Kingdom), and Philippe Van de Perre (Rwanda). Investigators: Anatolie Bazubagira (deceased) (Rwanda), Stéphane Blanche (France), Marc Bulterys (U.S.A.), John Chiphangwi (Malawi), Homer Davis (Haiti), Kevin De Cock (United Kingdom), Abel Dushimimana (Rwanda), Anatole Ekpini (Côte d'Ivoire), Joanne Embree (Canada), Carlo Giaquinto (Italy), Laura Guay (Uganda), Etienne Karita (Rwanda), Christian Kind (Switzerland), Marc Lallemant (Congo), Sophie Lallemant–Le Coeur (Congo), Marie-Jeanne Mayaux (France), Paolo Miotti (Malawi), Francis Mmiro (Uganda), Ruth Nduati (Kenya), Anuvat Roongpisuthipong (Thailand), Christine Rouzioux (France), Andrea Ruff (U.S.A.), Michael Saint-Louis (Zaïre), Nathan Shaffer (U.S.A.), Mauro Schechter (Brazil), Robert J. Simonds (U.S.A.), and Marleen Temmerman (Kenya). Statisticians: Daniel Commenges (INSERM U. 330, Bordeaux, France) and David Dunn (Institute of Child Health, London, United Kingdom).

The following persons participated also in the 1993 meeting of the Working Group on Mother-To-Child Transmission of HIV in Ghent (Belgium), September 3–5: Joan Casanova (EEC AIDS Task Force), Katrien Fransen (Belgium), Laurent Mandelbrot (France), Jorge Nieto (EEC AIDS Task Force), Roger Salamon (France), Rachid Salmi (France), Anna-Maria Stevens (Belgium), and Cladd Stevens (U.S.A.). A full report of the 1993 Ghent Workshop is available upon request.

Acknowledgment: This manuscript was prepared by Phillipe Msellati, Marie-Louise Newell, and François Dabis. This initiative was sponsored by the European Economic Community AIDS Task Force and the Global Programme on AIDS of the World Health Organization. The authors acknowledge the editorial assistance of the other members of the Scientific Secretarial and of Evelyne Bloch.

REFERENCES

1. Dabis F, Msellati P, Dunn D, et al. Estimating the rate of mother-to-child transmission of HIV. Report of a workshop on methodological issues, Ghent (Belgium), 17–20 February 1992. *AIDS* 1993;7:1139–48.
2. Newell ML, Peckham CS, Lepage P. HIV infection in pregnancy: implications for women and children. *AIDS* 1990;4 (suppl 1):S111–7.
3. Lallemant M, Le Coeur S, Samba L, et al. Mother-to-child transmission of HIV-1 in Congo, Central Africa. *AIDS* 1994;8:1451–6.
4. Adjorlolo-Johnson G, De Cock KM, Ekpini E, et al. Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. *JAMA* 1994;272: 462–6.
5. Datta P, Embree JE, Kreiss JK, et al. Mother-to-child transmission of human immunodeficiency virus type 1: report from the Nairobi study. *J Infect Dis* 1994;170:1134–40.
6. Bulterys M, Chao A, Dushimimana A, et al. Multiple sexual partners and mother-to-child transmission of HIV-1. *AIDS* 1993;7:1639–45.
7. Lepage P, Van de Perre P, Msellati P, et al. Mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) and its determinants. A cohort study in Kigali, Rwanda. *Am J Epidemiol* 1993;137:589–99.
8. Hom D, Guay L, Kenya-Mugisha N, et al. Natural history of HIV infection in Ugandan infants [Abstract no WeC 1058]. VIIIth International Conference on AIDS/III STD World Congress. Amsterdam, July 19–24, 1992.
9. Saint-Louis M, Kamenga M, Brown C, et al. Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic, and placental factors. *JAMA* 1993;269: 2853–9.
10. Halsey N, Boulos R, Holt E, et al. Transmission of HIV-1 infection from mothers to infants in Haiti. Impact on childhood mortality and malnutrition. *JAMA* 1990;264:2088–92.
11. Matheson PB, Weedon J, Cappelli M, et al. Comparative methods of estimating mother-to-child HIV-1 transmission rate [Abstract no PO-C16-2984]. IXth International Conference on AIDS/IVth STD World Congress, Berlin, June 6–11, 1993.
12. European Collaborative Study. Children born to women with HIV-1 infection: natural history and risk of transmission. *Lancet* 1991;337:253–60.
13. Blanche S, Rouzioux C, Moscato MG, et al. A prospective study of infants born to women seropositive for human immunodeficiency virus type 1. *N Engl J Med* 1989;320: 1643–8.
14. Kind C, Brändle B, Wyler C, et al. Epidemiology of vertically transmitted HIV-1 infection in Switzerland: results of a nationwide prospective study. *Eur J Pediatr* 1992;151:442–8.
15. Liomba G, Miotti P, Canner J, et al. Mortality experience in children of HIV-infected mothers in Malawi [Abstract no PoC4238]. VIIIth International Conference on AIDS/III STD World Congress. Amsterdam, July 19–24, 1992.
16. Van de Perre P, Lepage P, Homsy J, Dabis F. Mother-to-infant transmission of HIV by breast milk: presumed innocent or presumed guilty? *Clin Infect Dis* 1992;15:502–7.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete samples. *J Am Stat Assoc* 1958;53:457–81.
18. Newell ML, Peckham C. Risk factors for vertical transmission of HIV-1 and early markers of HIV-1 infection in children. *AIDS* 1993;7(suppl 1):S91–7.
19. Ryder R, Behets F. Reasons for the wide variation in reported rates of mother-to-child transmission of HIV-1 [editorial]. *AIDS* 1994;8:1495–7.
20. Report of a Consensus Workshop, Siena, Italy, January 17–18, 1992. Maternal factors involved in mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr* 1992;5:1019–29.
21. Dabis F, Msellati P, Newell ML, et al. Methodology of intervention trials to reduce mother-to-child transmission of HIV with special reference to developing countries. *AIDS* 1995 (in press).