

Letters to the Editor

Zidovudine to prevent mother-to-infant HIV transmission in developing countries: a view from Thailand

Sirs, The title of the September 1998 editorial of *Tropical Medicine and International Health* asks, 'Zidovudine to prevent mother-to-infant HIV transmission in developing countries: any questions?' (Van der Stuyft *et al.* 1998). We are five nurses, a social worker and a doctor working with (mostly poor) HIV-infected pregnant women in Bangkok and we would like to balance the technocratic approach of the editorial with a view from the field.

There are arguments in the editorial which are implied rather than clearly stated. These implications need to be clarified before the authors can embark on the critical appraisal which is their stated objective. There is the implication that providing short-course zidovudine (ZDV) is tantamount to sacrificing the mother's life in order to preserve that of the baby. Surely this is an exaggeration. Bridging the HIV control/AIDS care gap is described as a noble aim, but is dismissive of an initiative to reduce mother-to-child perinatal transmission in developing countries. We think that this particular initiative is about the only thing to emerge from the 12th World AIDS Conference which has some potential to narrow (slightly) the gap. Serious concerns are raised about the Bangkok perinatal ZDV study (Vuthipongse *et al.* 1998). These concerns are then dismissed without further discussion, even though the results of this study will have wide implications for policy in many countries. For example, following publication of results from the Bangkok perinatal ZDV study, UNAIDS, UNICEF and WHO launched a new initiative to limit mother-to-child transmission in 10 developing countries in Africa and Asia (WHO 1998). The implications of the editorial are dangerous because they carry the authority of an expert journal and the respected institutions with which the authors are affiliated.

The remainder of the editorial is clearly expressed opinion, referring to less developed countries as a uniform mass. Less developed countries are not all the same. Thailand has made a strong national response to AIDS (Phoolcharoen *et al.* 1998). Programmes to provide antiretroviral drugs (monotherapy and bitherapy) between 1992 and 1995 were costly with low effectiveness. A working team recommended in 1995 that antiretrovirals be reallocated to prevent vertical transmission (Phoolcharoen *et al.* 1995).

We share the editorial's concern about treatment for the mother after delivery. We know of a participant in the Bangkok perinatal ZDV study who has recently died. She had

symptomatic HIV infection when she first presented to an obstetrician in one of the CDC collaborating hospitals and was enrolled in the study. There was an eight-month delay before she was referred to a physician for investigation and treatment of her symptomatic HIV infection. For us as carers, it is difficult to accept the concept of researching a patient's condition without taking on responsibility for care and treatment.

Although there is a lack of tradition in many developing countries of structures to address ethical issues (Adler 1997), in Thailand these structures do exist and follow western models. The expatriate research industry and funding agencies have a responsibility to apply ethical standards to their work wherever it is done. Thai patients are being increasingly used for HIV/AIDS research. The research industry and funding agencies therefore have a particular responsibility in Thailand not to establish unethical precedents.

What is the next step for Thai women and their children, now that a study involving participation of HIV-infected pregnant Thai women has been published? Women need information to help them make the right choice for their situation. As can be seen from the above case, ethical problems do indeed remain to be considered, in particular how to set up a comprehensive model of care that pays attention to women's other health problems. However, the fact that AIDS programmes in countries such as Thailand are vertical rather than comprehensive is a donor-driven phenomenon.

Maybe the most important ethical consideration is the price of the drugs. The editorial refers to the generosity of the pharmaceutical industry in reducing the price of ZDV. How generous is Glaxo-Wellcome really being? The Wall Street Journal estimates that another 60 million US dollars a year will be added to Glaxo-Wellcome's revenue as a result of its generosity in 'discounting' ZDV for developing countries following publication of the Bangkok study results (Waldholz 1998). Should some of this 60 million dollars go towards paying for more generous support or care for study participants and their children?

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Zidovudine against mother-to-child HIV transmission

Sirs, In their editorial about the use of zidovudine to prevent mother-to-infant HIV transmission in developing countries, Van der Stuyft *et al.* (1998) mention the many obstacles to implementing such a programme and question the feasibility, acceptability, efficacy and cost of this intervention. We regret that the authors do not propose solutions to the incredible injustice that in industrialized countries we are well on our way to finding a cure for HIV infection while poor countries cannot even afford short-course therapy to prevent perinatal transmission of HIV. The question is not whether or not we should introduce antiretrovirals (ARVs) in resource-poor countries – the drugs are already available there, albeit only to a limited number of individuals at a very high price – and the pressure to obtain them will continue to increase. Certainly women will do everything they can to have a healthy child.

We agree that in order to use ARVs effectively and safely in low and medium-income countries, health services, including those for pregnant women, should be improved. Now, with the results of the Thailand study (Vuthipongse *et al.* 1998) showing the protective effect of zidovudine in preventing perinatal transmission of HIV, we have an excellent reason to do so. Initially zidovudine should be offered in situations where adequate care for pregnant women is already available or easily improved (for example, in medium-income countries or in health care facilities of large companies in resource-poor countries). This would provide valuable experience for large-scale introduction of ARVs.

It is difficult to prove, but we believe that AIDS research and AIDS control activities have had a positive effect on the control of other health problems: because of AIDS there is now increased interest in improving sexually transmitted dis-

ease and tuberculosis control programmes. AIDS boosted research in virology, immunology, pharmacology, epidemiology and social sciences. Development times for new drugs have been shortened. Hopefully, ongoing research of perinatal HIV transmission will lead to improved mother and child health care in general.

As physicians, rather than accept that health care budgets are divided for disease control according to the cost per DALY, we should fight to increase total health care budgets. More than 10 years of AIDS activism have shown that if HIV-infected individuals join forces with health care workers and scientists, politicians can be swayed and new donors found. People with HIV infection in poor countries should realize that potentially they are an enormous political force. Much has been achieved in the fight against HIV infection in a relatively short period of time, but not enough is reaching resource-poor countries. We cannot stop now. During the last years political leaders have made commitments: Clinton promised an HIV vaccine within 10 years, Chirac pledged to make ARV treatments available in Africa. At the next World AIDS Conference in Durban in the year 2000 we shall see how much of this has been accomplished.

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Zidovudine to prevent mother to infant HIV transmission in developing countries: many questions!

Sirs, We completely agree with the reaction of Kumphitak *et al.* (1998) to our editorial (Van der Stuyft *et al.* 1998). With one restriction: an in-depth discussion of the methodological caveats vis-a-vis the Bangkok perinatal Zidovudine study (Vuthipongse 1988) was – apart from not being our purpose – superfluous in the light of the CDC editorial accompanying the MMWR report on it. We acknowledge that a number of developing countries do fulfil the necessary prerequisites to successfully implement Zidovudine-centred control programmes of mother to infant HIV transmission. We also appreciate that the authors share our reservations with regard to the cost-effectiveness of such programmes and their operational feasibility.

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Most importantly, we are grateful that they substantiate our ethical considerations and our concern for the fate of the seropositive mothers. It may be noted in passing that the preliminary results of the PETRA-trial (37% reduction of vertical transmission after an antiretroviral regimen at delivery followed by a one week regimen for both newborn and mother – presented on 1 February 1999 at the Sixth Conference on Retroviruses, Chicago) do not substantially affect the nature of these apprehensions.

We also appreciate and support Colebunders and Coppeters (1999) militant activism for the rights of AIDS patients all over the world. However, we do not agree with their assumptions and premises on what constitutes the most effective health care model and the best political strategy to achieve more equity. Kumphitak's letter eloquently addresses the inherent drawbacks of vertical programmes, which have never been demonstrated to generate positive spin-off effects for the control of nontargeted health problems. Furthermore, health policy decisions driven by political eagerness to demonstrate commitment to the 'affordable' should not be encouraged, but countered with scientific evidence on what constitutes the right agenda. We fear that the current excitement about a tool that works will detract energy and resources while the key issues in AIDS research and control still remain unresolved. In view of the huge numbers of at risk and infected people in the developing world, the priority in AIDS research remains the search for a vaccine (Anonymous 1998) and for affordable treatment regimens for all HIV-infected people (UK NGO Consortium 1998). Survival of AIDS patients in the developing world has not improved, and will not do so, as long as effective drugs are inaccessible. Should this problem not be tackled at its roots instead of shifting into seemingly rewarding programmes?

It was our intention to signal, somewhat provocatively, that the Bangkok perinatal Zidovudine trial raises quite a few questions that deserve thoughtful consideration. Some understatement on the 'generosity' of the pharmaceutical industry, among others, may not have been fully appreciated, but our more outspoken challenges seem to have elicited the reflection we hoped for.

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Relationship between histopathological findings and phylogenetic divergence in *Trypanosoma cruzi*

Sirs, recently de Diego *et al.* (1998) showed in an interesting study that different genotypes of *Trypanosoma cruzi* can provoke distinct histopathological lesions in the mouse. The authors draw special attention to the varieties of cardiac and brain tropism of *T. cruzi* and conclude that the histological patterns found in the experiments could explain, in part, differences of the clinical features of patients with Chagas' disease. We would like to remember that these experimental results are not only consistent with the well-known varieties of the clinical appearance in patients but also with the differences of the morphological findings in patients suffering from Chagas' disease.

We studied the histopathologic pattern in patients with chronic Chagas' disease, who suffered lethal reactivation caused by a secondary immunodeficiency during chemotherapy (in patients with malignant neoplasms) or provoked by infection with HIV (Metze *et al.* 1991, 1993; Metze & Maciel 1993). Careful and detailed histological examinations of the organs at autopsy, complemented by immunohistochemical or electron microscopic studies when necessary, disclosed three distinct forms of reactivation: (i), acute Chagas' meningoencephalitis with the presence of pseudocysts, but without myocarditis and without areactive pseudocysts of *T. cruzi* in the myocardium; (ii), acute reactivated chronic Chagas' myocarditis with abundant pseudocysts but no cerebral lesions (neither inflammatory alterations nor necrosis or pseudocysts); and (iii), acute Chagas' meningoencephalitis and reactivated myocarditis, both with the presence of pseudocysts of *T. cruzi*.

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To explain these results we postulated that differences of the histological pattern of reactivated Chagas' disease could have been caused by varieties of the tissue tropism of *T. cruzi* (Metze & Maciel 1993). This is in accordance with the investigations of de Diego *et al.* (1998) who revealed that genotype 20 showed a marked tendency to encephalitic lesions in mice with liquefied necrosis but only scanty foci in the heart, whereas 83% of studied stocks of genotype 39 showed pseudocysts in the heart, but fewer lesions in the brain.

In summary, we think that the animal experiments conducted by de Diego *et al.* (1998) corroborate well our previously postulated hypothesis, which had been established on histological findings of patients with recrudescence of Chagas' disease.

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Clinical and biological manifestations of dengue

Sirs, in their analysis of clinical and biological manifestations of dengue in the November issue, Deparis *et al.* (1998) conclude that the 'association of macular rash, pruritus, low platelet count and leukopenia is clinically not predictive of dengue fever'. We think this conclusion should be modified.

Clinical signs and symptoms almost never are 100% predictive or pathognomonic of a disease. Instead, we look for relative proofs of the presence or absence of disease, represented by their positive and negative likelihood ratios. The two combined constitute the odds ratio, which gives a fair representation of the overall discriminatory value of a sign or symptom (Dujardin *et al.* 1994). Odds ratios and likelihood ratios are determined on the basis of cases and controls who belong to the same population, e.g. 'all patients with fever', 'all patients presenting with fever and myalgia'. In this study the definition of the inclusion criteria as 'all patients in whom the diagnosis of dengue was suspected' is not only too vague a description for estimation of likelihood ratios that can be extrapolated to

other clinical situations, but moreover, inclusion criteria are subsequently themselves analysed for their predictive power. As some clinical signs contribute to suspicion, such as macular rash and pruritus, patients presenting such signs are more likely to be enrolled in the study, both for dengue and non-dengue groups. Obviously this may be confounding by decreasing the specificity of the concerned arguments.

In contrast to what the authors ascertain, we could not find a true analysis of the value of the association of the four key signs. The positive predictive value is given for 'the clinical diagnosis', without specification, and the presentation of the utility of the results of the logistic regression is based on an 'and/or' string of four characteristics, which is not correct. It would mean that the presence of only one of the four symptoms e.g. pruritus, would increase the probability of dengue, notwithstanding the absence of the others. Further analysis might have revealed that the combination of three or four signs predicts almost perfectly dengue fever, or that absence of one or two signs excludes it.

It should be emphasized that the positive predictive value the authors found is quite high, at least partially thanks to the high pretest probability in case of an epidemic. However, for the diagnosis of dengue fever we need a certainty of 100%, as most cases have a relatively mild course and therapy is absent (Kassirer 1989). The only advantage of a clinical diagnosis would be the warning of risk of complications. Therefore, the problem is not to decrease the false positive rate of the clinical diagnosis which is already low (1/3), but rather to decrease the false negative rate, i.e. dengue cases wrongly excluded from the physicians's diagnosis. If there is no clinical characteristic with a good negative likelihood ratio (LHR-), any fever should be considered to be dengue during an epidemic.

In conclusion, we agree that the inclusion criteria permit calculation of the positive predictive value of a clinical diagnosis of dengue fever relative to the gold standard of laboratory confirmation, but we disagree that they are appropriate for analysis of the predictive value of disease characteristics. Further, no true analysis of the association of clinical signs was worked out. Finally, as the diagnostic threshold is rather low, research efforts should concentrate on avoiding false negatives, hence on finding clinical signs with a significant negative likelihood ratio.

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Erratum

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Towards a kala azar risk map for Sudan: mapping the potential distribution of *Phlebotomus orientalis* using digital data of environmental variables

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Page 110: Figure 2. Due to a typographical error the legends for panels a, b and d and the labels for panel d were omitted. Figure 2, including the legends and labels, is reproduced opposite.