CORRESPONDENCE

Preventing HIV-1: lessons from Mwanza and Rakai

Sir—Observational studies early in the HIV-1 epidemic showed the strong relation between sexually transmitted disease (STDs) and HIV-1 infection.[1] By causing inflammation, ulceration, or both, in the genital tract, STDs increase the shedding of HIV-1 in men and women and may also increase susceptibility to HIV-1 infection.

The community randomised trial in Mwanza, Tanzania, showed that improved syndromic management of STDs in primary health care reduced the rate of HIV-1 infection by about 40% in rural communities.[2] This intervention showed only a slight impact on the overall prevalence of most treatable STDs, many of which were symptomless, but a striking impact on the prevalence of symptomatic urethritis in men and of new cases of active syphilis.[3] The investigators concluded that the impact of the intervention on HIV-1, transmission was due to a reduction in the duration of symptomatic STDs, which are more likely than symptomless infections to increase the shedding of and susceptibility to HIV-1.

Maria Wawer and colleagues (Feb 13, p 525)[4] measure the effect of STD control by periodic mass treatment for bacterial and protozoal STDs on HIV-1 infection in Rakai District, Uganda. Between rounds of mass treatment, little or no effective treatment for STDs seems to have been available to these communities. There was no difference in incidence of HIV-1 between the intervention and comparison communities after 20 months. Penny Hitchcock and Lieve Fransen, in their accompanying commentary,[5] attribute the results obtained in the two studies to the different stages and dynamics of the HIV-1 epidemic in the two areas. We propose another explanation.

Periodic mass treatment of the general population is not an effective strategy for STD control. The communities studied in Rakai had year-round road access. People living there probably travel frequently, and may have sexual encounters outside their communities, leading to continuous reintroduction of STDs between treatment rounds.

In support of our hypothesis, after 20 months of follow-up the intervention group only showed a significant reduction in trichomoniasis and serological evidence of syphilis, and no difference was seen for all the other STDs targeted. The treatment given to most adults (single-dose azithromycin, ciprofloxicin and metronidazole), should be highly efficacious against most bacterial STDs and reduce the prevalence of gonorrhoea and genital chlamydia to almost zero. Yet in the intervention group, only slight reductions in prevalence of STDs were achieved after two rounds of mass treatment. Mass treatment once every 10 months did not stop STD transmission. Moreover, coverage of mass treatment was incomplete: 80% of eligible residents received the treatment at each round, but fewer than 70% of enumerated residents were covered.

Mass treatment of communities as a public-health strategy for STD is difficult in terms of logistics, sustainability, cost, emergence of resistance among other pathogens, and may also undermine existing health-care and prevention structures. Prevention is of the utmost importance in the developing world. Provision of effective treatment for symptomatic STDs has been shown to prevent HIV-1 infection. The results of the Rakai study, which assessed a different intervention, must not be used as an excuse to cut back on the resources made available for STD control.

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2 Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in Tanzania: a randomised controlled trial. *Lancet* 1995; **346:** 530–36.

3 Mayaud P, Mosha F, Todd J, et al. Improved treatment services significantly reduce the prevalence of sexually transmitted disease in rural Tanzania: results of a randomised controlled trial. *AIDS* 1997; **11:** 1873–80.

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5 Hitchcock P, Fransen L. Preventing HIV infection: lessons from Mwanza and Rakai. *Lancet* 1999; **353:** 513–15.

Sir—In their Feb 13 commentary, Penny Hitchcock and Lieve Fransen[1] discuss the seeming discrepancy between the results of the Mwanza study[2] which showed an effect on HIV-incidence of STD treatment, and the findings by Maria Wawer and colleagues[3] from Rakai where no effect on HIV-1 infection of such treatment was observed. They suggest a possible explanation relating to the difference in the maturity of the infection, the Mwanza results being an example of a short-term impact of STD prevention and control in an immature epidemic (HIV prevalence 4%). By contrast, the Rakai study could reflect the short-term impact in a mature epidemic (HIV prevalence 16%). There are, however, also other explanations that should be considered.

Wawer and co-workers state, with reference to table 3 in their report, that at round 1, rates of syphilis, trichomonas, bacterial vaginosis, and reported STD symptoms in the previous year were similar in the intervention and control group. However, prevalence ratios (intervention versus control group) for gonorrhoea and chlamydia infection were 2·5 and 1·5, respectively. Further, at enrolment a larger proportion of the intervention than the control group reported two or more partners the previous year, having sex partners more than 5 km away, ever having used condoms, and use of alcohol in the previous month. Similar differences were also observed at follow-up. Thus, a larger proportion of the intervention group reported high risk behaviours that were also shown in the Rakai study (table 5) to be associated with increased HIV-1 incidence. Thus, without any intervention, it is to be expected that the intervention group at follow-up would have a higher HIV-1 incidence than the control group. An observation of similar incidence at follow-up may thus still indicate an effect of the intervention.

Both the intervention and control

groups received identical education on condom use and prevention of HIV-1 infection. Further, controls with STD symptoms at enrolment received treatment, and all participants were encouraged to seek care if they had symptoms of STD between the survey rounds. Thus, the control group benefited from intervention activities that would tend to keep the difference between the intervention and control groups to a minimum.

On this background I fully agree with the conclusion given by Hitchcock and Fransen that anything other than a sustained commitment to STD prevention as an important part of HIV-1 control programmes is unthinkable.

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1 Hitchcock P, Fransen L. Preventing HIV infection: lessons from Mwanza and Rakai. *Lancet* 1999; **353:** 513–15.
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3 Wawer MJ, Sewankambo NK, Serwadda D, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *Lancet* 1999; **353:** 525–35.

Sir—Penny Hitchcock and Lieve Fransen[1] provide a plausible epidemiological explanation for the strikingly negative results of Maria Wawer and colleagues' STD prevention trial[2] on HIV-1 incidence rates in Rakai Uganda. Nevertheless, Hitchcock and Fransen go on to recommend that STD prevention programmes should be equally implemented in similar contexts with mature HIV-1 epidemics. They are of course right, for Wawer's negative result in a community intervention trial will not withhold us from preventing and treating STDs. We might, however, still want to reflect a bit on the design of such a STD prevention programme.

Our experience in communicable disease control in the Great Lakes area, makes us concerned about the consequences of large-scale distribution of ciprofloxacin in areas where multiresistant shigellosis is endemic.[3] Furthermore, on the basis of data provided by Wawer and co-workers and current generic drug prices, we estimate the drug cost for one course of their intervention regimen to be US$22.50. Applying this drug scheme every 10 months to all participants aged 15–59 years in the Rakai community would thus amount to $5 184 000 for drugs only.

Mass treatment by the project team, with exclusion of prior household census, took reportedly 1 month to complete per cluster (about 1330 people). Extrapolation of this workload to the total Rakai district adult population amounts to 144 months' work, or at least 22 mobile teams to employ simultaneously and full time. The running cost to maintain one mobile team for Uganda's sleeping sickness programme is currently estimated at $3500 per month (M Gastellu-Etchegorry, personal communication), which brings a minimum estimation of the running cost for the STD intervention to about $15 per inhabitant per year. The World Bank estimated that Uganda's total health expenditure per inhabitant was $10 in 1994.[4] Given current health-service budgets in the countries the intervention is supposedly designed for, we were puzzled to read that Hitchcock and Fransen described this intervention as "feasible" and "affordable".

Considering the comprehensive package of quality health-care services that could have been provided to Rakai district for the budget allocated to this study, is it ethical to undertake a community trial if researchers know that its results, whether positive or negative, will not alter current control policies anyway? Moreover, is it ethical to undertake community trials to test interventions that are, from a public-health perspective, unsafe, unfeasible, and unaffordable for that same community? This question was also raised by the Perinatal HIV Intervention Research in Developing Countries Workshop Participants (March 6, p 832).[5] We wonder whether African communities have any power to oppose this kind of epidemiological research.

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1 Hitchcock P, Fransen L. Preventing HIV infection: lessons from Mwanza and Rakai. *Lancet* 1999; **353:** 513–15.
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5 Perinatal HIV Intervention Research in Developing Countries Workshop Participants. Science, ethics, and the future of research into maternal infant transmission of HIV-1. *Lancet* 1999; **353:** 832–35.

Authors' reply

Sir—Angus Nicoll and colleagues suggest that the divergent results of the Mwanza and Rakai STD control trials for AIDS prevention were due to the interventions used: syndromic treatment in the former study and mass treatment in the latter. It is unlikely that a syndromic approach would have had substantial effects on HIV-1 in Rakai, where most HIV-1 transmission occurred independently of STD symptoms or laboratory diagnoses. In addition, the sensitivity and specificity of symptoms of STD screening were poor[1] (as has also been reported in Mwanza).[2] Finally, many symptoms in the Rakai population were not due to treatable STDs: 42% of genital ulcers were herpes simplex virus-2, and only 7% were identified as syphilis or chancroid; over 50% of women had bacterial vaginosis, a disease which is not amenable to cure and is associated with risk of HIV-1.[3] The hypothesis that the Mwanza trial achieved success by reducing symptom duration is attractive, but data on duration were not reported in that study. Finally, reintroduction of STDs in Rakai may have diluted an effect; however, in a substudy of pregnant women in whom STDs were significantly reduced in the intervention compared with the control group, we observed no reduction in HIV-1 incidence.

Gunnar Kvåle suggests that the Rakai results may have been due to lack of comparability between groups, or to the services offered to the control population. Absolute differences between groups in the distribution of key variables were small, and were adjusted for in analyses. Condom use was low in both groups, and only 16% of patients with symptoms in the control group reported seeking effective treatment. Thus, ethically mandated services cannot explain the negative results in the overall population or in all subgroups.

Francine Matthys and Marleen Boelaert raise issues of drug resistance and costs. Medications were provided as single, directly observed treatment, to keep inadequate compliance, a main cause of selective resistance, to a minimum. Gonorrhoea sensitivity testing identified no resistant strains. The drug costs estimated by Matthys and Boelaert are excessively high: metronidazole, ciprofloxacin, and penicillin together cost under US$1 in Kampala pharmacies. These drugs are also included in the Uganda Ministry of Health standard drug regimen, where their combined cost is even lower. Azithromycin is being used in mass treatment trachoma campaigns in developing countries, and prices are

falling.

Matthys and Boelaert do not distinguish between efficacy trials that show proof of concept and operations research that test programmatic strategies. Efficacy trials identify which therapeutic or preventive measures have desired health effects and warrant additional feasibility research; such trials are crucial for sound health policy and resource allocation.

Matthys and Boelaert also raise ethical questions. The Rakai trial was conducted by the Uganda Ministry of Health/Uganda Virus Research Institute, and researchers at Makerere, Columbia, and Johns Hopkins Universities. The trial was approved by human subjects boards in all collaborating instutions and was fully explained to individuals and communities. Participation was completely voluntary. As discussed by Mbidde,[4] African researchers and policy makers are fully aware of ethical issues and of the need to conduct studies that will provide data appropriate to local circumstances. Our results from Rakai, including the beneficial effects of STD mass treatment in pregnancy on maternal and infant health, are under consideration by the Uganda Ministry of Health to determine policy implications.

In accordance with previous studies, Rakai showed associations between STDs and HIV-1 infection at the individual level. We agree that STD control is important to reduce the risk of HIV-1 for individuals, provide reproductive health benefits, and in some settings potentially to reduce population incidence of HIV-1 infection. In this context, it should be noted that neither Rakai nor Mwanza achieved optimum STD results. We are currently collaborating with Mwanza researchers to model better approaches to STD control; among the models being looked at are combined syndromic and mass treatment approaches.

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1 Paxton LA, Sewankambo N, Gray R, et al. Asymptomatic non-ulcerative genital tract infections in a rural Ugandan population. *Sex Transm Infect* 1998; **74:** 421–25.

2 Grosskurth H, Mayaud P, Mosha F, et al. Asymptomatic gonorrhea and chlamydia infection in rural Tanzanian men. *BMJ* 1996; **312:** 277–80.

3 Taha T, Hoover DR, Dallabetta GA, et al. Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition. *AIDS* 1998; **12:** 1699–706.

4 Mbidde E. Bioethics and local circumstances. *Science* 1998; **279:** 155.

Immunotherapy for colon cancer

Sir—We do not entirely agree with J B Vermorken and colleagues' (Jan 30, p 345)[1] conclusion that "ASI [active specific immunotherapy] gave significant clinical benefit in surgically resected patients with stage II colon cancer". The separate analyses of pathological stage were prespecified in the study protocol, but comparison of patient characteristics was based on the two initial groups. This discrepancy is of particular importance because the investigators emphasise that "there was a disproportionate number of non-disease-related deaths among non-treated patients compared with vaccinated patients". Therefore, the significant result in stage II patients' survival may be attributable to these non-disease-related deaths—ie, age-related cardiovascular deaths—and not to the treatment. Furthermore, Vermorken et al note in table 2 that "deaths of unknown causes were scored as disease related". This decision may have modified the results and they should have indicated the exact number of deaths from unknown causes. Medical practitioners generally accept that death of a patient previously treated for cancer, without evidence of recurrence, is probably due to other causes and not to the cancer itself.

Vermorken and co-workers state that "16 vaccinated patients were ineligible" and that 21 patients did not receive all four vaccinations. Since they insisted on all four vaccinations with a 6-month booster, they would have excluded a high proportion of the vaccination group. We also noted a discrepancy between the methods (they needed a 515 patient sample over 5 years) and the patient population mentioned (254 patients over 10 years). A delayed period of inclusion often produces bias, because management changes over a 10-year period. Moreover, the follow-up was very varied and an 8-month follow-up is not sufficient in such a disease.

Was chemotherapy in fact offered as treatment for stage III patients, as suggested by Migdley and Kerr?[2] Vermorken's report does not contain sufficient proof to justify the use of ASI in the management of stage-II colon cancer, even with minimum adverse reactions.

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1 Vermorken JB, Claessen AME, van Tinteren H, et al. Active specific immunotherapy for stage II and stage III human colon cancer: a randomised trial. *Lancet* 1999; **353:** 345–50.

2 Migdley R, Kerr D. Colorectal cancer. *Lancet* 1999; **353:** 391–99.

Sir—J B Vermorken and co-workers[1] report beneficial effects of active specific immunotherapy in colon carcinoma, particularly in stage II. We question some of their conclusions. The accrual period was 10 years with a median follow-up of 5·3 years. Many cases were followed for a time (as little as 8 months) that was insufficient to evaluate treatment outcome. They blame tumour burden in stage III disease for the absence of vaccination benefit. However, vaccination was started only 1 month after radical resection, when tumour burden generally encompasses microscopic distant metastases, in both stage II and III patients. Moreover, patients with stage III disease made up less than a third of the 126 vaccinated patients and, as expected, recurrence rates were higher in this subgroup. These two factors could explain why a beneficial effect in stage III patients was not significant.

The investigators draw conclusions on the basis of a subgroup analysis of apparently mismatched vaccination and control groups. What else could account for the difference in non-disease-related deaths—59% and 39%, respectively? According to table 1 age cannot be the explanation. Finally, the whole group might not be representative of the average patient with colon carcinoma, since performance status 0 and 1 patients only were eligible. According to Vermorken and colleagues, side-effects were unimportant and quality of life good. Why, then, did less than 79% of patients finish their course of vaccination?

Vermorken et al strongly advocate their booster after 6 months as a crucial restimulation that may have increased substantially the anti-tumour effect. However, outcome in a similar but smaller trial,[2] in which the booster was not given, showed ratios between vaccinated and non-vaccinated patients that were close to those presented by Vermorken.