

scale up screening blood for transfusion. Partner reduction is the intended effect of multiple prevention actions that include youth education, social mobilisation to change sexual behaviour norms, and combating the unequal gender and economic order that sustains multiple and concurrent partnerships and age-disparate relationships.

And when Wilson and Halperin endorse "saturation coverage of vulnerable groups" in concentrated epidemics but are dubious about "participatory consultative approaches", they seem to have in mind some unspecified, non-participatory, non-consultative intervention proven to change behaviours. To be effective, HIV prevention programmes for sex workers, injecting drug users, or men who have sex with men need to address immediate risk settings as well as social norms and regulatory environments. No quick fix can substitute for the sustained political will needed to ensure these populations are not dehumanised.

Our call to action² to fully implement combination prevention is framed in terms of accepting its complexity: neither paralysed in the face of vast social inequities nor tempted by magic bullet solutions. A revitalised HIV prevention movement needs to move beyond its fixations about whether any specific intervention is more important than the other while ignoring how to achieve them.

This is an argument for more priority setting by countries, not less. We have to bridge the evidence gap concerning the synergistic effect of complementary prevention activities in real-world situations, not jettison major parts of the prevention response because their effect in isolation is insufficiently proven.

If we really want to advance the effectiveness of HIV prevention, we have to disabuse ourselves of the notion that the epidemic can be conquered by a single best intervention. Rather, we must focus on scaling up combination efforts and on building the evidence base for

which mixes produce maximum effect in which settings.

We declare that we have no conflict of interest.

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- 1 Wilson D, Halperin DT. "Know your epidemic, know your response": a useful approach, if we get it right. *Lancet* 2008; **372**: 423–26.
- 2 Piot P, Bartos M, Larson H, Zewdie D, Mane P. Coming to terms with complexity: a call to action for HIV prevention. *Lancet* 2008; **372**: 845–59.

HIV transmission under highly active antiretroviral therapy

In their model-based analysis, David Wilson and colleagues (July 26, p 314)¹ predict that the risk of HIV transmission in the presence of effective treatment is low but non-zero, and that use of condoms should still be advised, contrary to advice issued in January, 2008, by the Swiss Commission on AIDS.²

There are several flaws in the analysis by Wilson and colleagues. First, when applying their model to an untreated homosexual couple, we calculate a risk of transmission of 60% after 1 year (100 sexual contacts). That seems extraordinarily high, and contrary to published data and experience.³ Second, Wilson and colleagues state: "Under our assumptions, the effect-

iveness of treatment in reducing the risk of HIV transmission per sexual act was about the same as has been reported for condoms." Therefore, even with their high estimates, Wilson and colleagues confirm the Swiss statement and even document a higher risk for condom use (without treatment) than for treatment alone.

Finally, the major limitation is the neglect of the role of sexually transmitted diseases (STDs), which are well known to fuel the HIV epidemic.⁴ In the Rakai study,⁵ genital discharge and dysuria were associated with increased risk of transmission. Thus, transmission figures in the presence of STDs overestimate the residual risk under HAART in the absence of STDs.

Since the "Swiss statement" is often misinterpreted, we would like to re-emphasise the main point. The risk of sexual transmission of HIV is negligibly low if three conditions are met: (1) the HIV-infected patient is receiving antiretroviral therapy with excellent adherence; (2) blood viral load has consistently been undetectable (<40 copies per mL) for more than 6 months; and (3) no STDs are present in either of the partners. The statement also made it clear that it is up to the HIV-negative partner to decide whether he or she wants to stop using condoms with the treated partner and accept the residual risk.

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- 1 Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet* 2008; **372**: 314–20.
- 2 Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes séropositives ne souffrent d'aucune autre MST et suivant un traitement antiretroviral efficace ne transmettent pas le VIH par voie sexuelle. *Bull Med Suisses* 2008; **89**: 165–69.



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- 3 DeGruttola V, Seage GR, Mayer KH, Horsburgh CR Jr. Infectiousness of HIV between male homosexual partners. *J Clin Epidemiol* 1989; **42**: 849–56.
- 4 Wasserheit J. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis* 1992; **19**: 61–77.
- 5 Quinn TC, Wawer MJ, Sewankambo N, et al, for the Rakai Project Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342**: 921–29.

Authors' reply

The authors of the "Swiss statement" assert that the risk of HIV transmission from people on effective antiretroviral therapy is negligible, despite the absence of studies large enough to provide empirical evidence. Although determination of viral titres in source partners is not typical practice, cases of transmission from effectively treated people have been reported.¹ Furthermore, although HIV might be undetectable in blood, it can be present in semen or genital fluids at infectious amounts.²

By use of a relation between viral load and transmission risk³ derived from the Rakai study,⁴ we found that the exposure per risk is small but non-zero. Because it accumulates over multiple exposures,⁵ it is not surprising that the cumulative risk among serodiscordant homosexual men becomes large after 100 unprotected receptive anal intercourse exposures. This risk is reduced to 4–5% with condoms or treatment, but 0.22% with the safer alternative of condoms and treatment. Under the relation used in our paper, effective treatment reduces a baseline viral load of 10^{4.5} copies per mL to 10 copies per mL—an estimated efficacy of 96%, which is similar to condoms (assumed 95%). Various factors might reduce the effectiveness of treatment, including the degree of viral suppression, treatment failure, viral blips, and the presence of other sexually transmitted infections (STIs). Thus, treatment can complement consistent condom use but should not replace it.

We used the best evidence available on the HIV transmission risk without

STIs. The relative reduction in risk due to treatment was estimated from the Rakai study.⁴ In our analysis we conservatively assumed that the three conditions of the Swiss statement hold, including no other STIs.⁵ However, if other STIs are present, baseline risk is higher and an incidence even greater than our predicted estimates could be expected.

For global HIV prevention, there is a major difference between small and zero risk. At an individual level, the HIV transmission probability per exposure might seem small. Nevertheless, it is equal to the best estimate of the transmission probability that has resulted in tens of millions of cases of HIV globally. We suggest that statements of non-infectiousness under effective treatment are not only scientifically inaccurate, but could impede efforts to mitigate HIV incidence if they lead to the abandonment of condoms. We encourage clinical researchers internationally to join forces to investigate the risk of transmission from people undergoing effective antiretroviral treatment.

We declare that we have no conflict of interest.

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- 1 Sturmer M, Doerr HW, Berger A, Gute P. Is transmission of HIV-1 in non-viraemic serodiscordant couples possible? *Antivir Ther* 2008; **13**: 729–32.
- 2 Kalichman SC, Di Berto G, Eaton L. Human immunodeficiency virus viral load in blood plasma and semen: review and implications of empirical findings. *Sex Transm Dis* 2008; **35**: 55–60.
- 3 Smith RJ, Blower SM. Could disease-modifying HIV vaccines cause population-level perversity? *Lancet Infect Dis* 2004; **4**: 636–39.
- 4 Quinn TC, Wawer MJ, Sewankambo N, et al, for the Rakai Project Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342**: 921–29.
- 5 Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet* 2008; **372**: 314–20.

COMET results are not stellar

The COMET study by Paul Emery and co-workers (Aug 2, p 375)¹ shows that methotrexate plus etanercept is superior to methotrexate alone for several outcome measures in recent-onset rheumatoid arthritis. However, methotrexate monotherapy is known to be inferior to combination treatment with disease-modifying antirheumatic drugs (DMARDs).^{2,3} Therefore, the trial design renders the results of little use for evidence-based rheumatology practice, which should begin with combinations of conventional DMARDs.

A related issue is an ethical one in that treatment of patients with early rheumatoid arthritis with methotrexate monotherapy for 1 year denies the participants a treatment known to be superior—ie, combination DMARD therapy.

Also, despite a comparator group known to be inferior to current best practice, the efficacy results are modest. Although Emery and colleagues describe the "positive clinical outcomes in the combination group", the results for this group are disappointing when one considers cost and benefit. Only 50% achieved remission at 1 year with methotrexate in combination with etanercept—a biological agent that in Australia costs about AUS\$24 000 (US\$19 000) per patient per year. This contrasts with studies of methotrexate in combination with the very much cheaper DMARDs sulfasalazine and hydroxychloroquine, for which remission rates of 65% at 18 months² and 47–54% at 1–3 years⁴ have been reported.

Early pivotal registration trials for biological agents used methotrexate monotherapy as a comparator. However, knowledge of effective DMARD use has increased to the extent that methotrexate monotherapy in established, or early, rheumatoid arthritis should no longer be accepted by regulators or research ethics committees as a comparator for trials of biological agents.



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