significantly lower with VBT than with EBRT both during and up to 24 months after treatment. Moreover, previously reported quality-of-life data from the PORTEC-2 trial[8] showed that VBT was associated with lower symptom scores for diarrhoea and faecal leakage than was EBRT, allowing improved social functioning and reduced restriction on daily activities. Notably, the rising tide of morbid obesity is not only responsible for the increasing incidence of this disease, but also makes EBRT more challenging to deliver.

The central post-hoc pathology review in today's study deserves comment. Review resulted in reclassification of 14% of randomly assigned patients as ineligible according to protocol, although secondary analysis of strictly eligible patients did not change the outcome. Use of immediate expert pathology review in all trials represents good specialist practice, and would avoid randomisation of ineligible patients. Furthermore, in a routine setting, such practice might avoid use of inappropriate and potentially toxic therapy in a substantial proportion of cases.

We believe that the results of PORTEC-2 are reliable and clinically important. We agree with the investigators' recommendation that VBT should become the standard of care for women with endometrial cancer of intermediate and high-intermediate risk. VBT is not as widely available as is EBRT so patients might need to travel further for treatment, but VBT needs fewer treatments and has a better toxicity profile than does EBRT, and is associated with improved quality of life for a similar outcome. What of high-risk early disease and locally advanced disease? New trials need to address key issues—eg, does EBRT have any benefit, and can chemotherapy offer a survival improvement? The continuing PORTEC-3 trial,[9] comparing EBRT alone with chemoradiation followed by chemotherapy, is attempting to answer these questions. Successfully undertaken clinical trials are now defining treatment strategies in endometrial cancer, and collaborative trials will be crucial to achieve much needed advances for improved outcomes. PORTEC-2 is a substantial contribution towards that goal.

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Treating HIV infection with drugs for HSV-2 infection?

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Jairam Lingappa and colleagues,[1] in *The Lancet* today, present results from the Partners in Prevention HSV/HIV Transmission Study. This study was in HIV-1 discordant couples, and the primary objective was to directly assess the efficacy of suppressive therapy with aciclovir in reduction of onward transmission of HIV-1 from partners co-infected with herpes simplex virus type 2 (HSV-2). In the past few years, other placebo-controlled trials have studied the effects of aciclovir or valaciclovir on HIV-1 transmissibility, with genital shedding of HIV-1 RNA as a proxy of transmissibility.[2-6] In these trials, suppressive therapy

of HSV-2 reduced genital shedding of HIV-1 RNA. However, the Partners in Prevention Study showed that suppressive therapy with aciclovir did not reduce onward transmission of HIV-1.[7]

In randomised trials,[2–6] researchers identified that there could be a clinical benefit because suppressive therapy with aciclovir or valaciclovir seemed to lower HIV-1 RNA plasma levels in co-infected patients. In view of the fact that HIV-1 plasma viral load is related to disease progression, this finding opened up new perspectives for the management of HIV-infected patients. A meta-analysis[8] of randomised trials done in industrialised countries in the early 1990s reported that aciclovir offered a survival benefit to HIV-infected patients. Today's report is the first to assess the effects of suppressive therapy for HSV-2 on disease progression in patients co-infected with HIV in sub-Saharan Africa during a 2-year period. In patients assigned to aciclovir, fall of CD4 cell count was slower, start of antiretroviral treatment was delayed, and mortality was reduced, compared with patients in the control group. These findings are exciting, but are we ready to translate them into new guidelines for the management of such co-infected patients?

WHO recently revised its guidelines for the treatment of HIV-infected patients in low-income and middle-income countries.[9] In line with the recommendations of the International AIDS Society, WHO recommends that antiretroviral treatment is started at a CD4 cell count of 350 per μL. These new guidelines imply that resources for HIV care in countries of low and middle incomes will have to increase substantially, which is unlikely to happen in the present economic crisis.[10] Treatment of HIV-infected patients with drugs that are cheap and easy to take, and which slow disease progression, is thus an appealing strategy to save on antiretroviral treatments. Does suppressive therapy of infection with HSV-2 fit this bill? Lingappa and co-workers are cautious and suggest that further studies are needed. There are unresolved issues, and translation of results of this study into real-life programmes would be premature.

In patients assigned to aciclovir, the incidence of selected endpoints for HIV-1 disease progression was 16% lower than in patients assigned to placebo. With the assumption that disease progression continued on the same course after the 24 months of the trial, an estimated median time to CD4 cell count of fewer than 350 per μL was delayed by 6·3 months. However, data suggest that, to have an effect on HIV disease progression, at least 90% of the prescribed doses of aciclovir need to be taken. Adherence to the study drugs was high in today's trial but such high levels of adherence will be difficult to achieve in real life on a large scale, because most co-infected patients have asymptomatic herpes infection and will not feel any immediate benefit from taking aciclovir. Efforts to convince these patients to adhere to suppressive therapy might be out of proportion to the expected gains, and cost-effectiveness analyses are needed to resolve this question.

Additionally, suppressive therapy for HSV-2 is not the first prophylactic treatment that has been assessed. In the 1990s, before antiretroviral therapy became widely available in low-income and middle-income countries, several prophylactic treatments were assessed in HIV-infected patients with the aim to slow disease progression.[11–14] Nowadays, interest has been renewed in the development of care packages given before HIV antiretrovirals, but the focus has somewhat shifted. In many settings, especially in sub-Saharan Africa, concern is growing that patients who have been tested and diagnosed with HIV infection are lost to follow-up and present later with advanced HIV infection.[15,16] A care package given before HIV antiretrovirals could serve a dual purpose: to ensure that people remain under care and start HIV antiretrovirals

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before they are severely immunocompromised, and to slow disease progression.

Such a package could include cotrimoxazole and isoniazid preventive therapy, regular CD4 cell counts, nutritional support, anthelmintic drugs, multivitamins, and insecticide-treated bednets for the prevention of malaria. All these components have adherence issues, and before advocating for an additional possible intervention, such as aciclovir suppressive treatment, we need to define and assess the relative contribution and the specific target group of every component and its cost-effectiveness in retention of patients and delay of disease progression.

Further research is needed on the feasibility and cost-effectiveness of suppressive therapy for infection with HSV-2 as a strategy to slow disease progression in HIV-co-infected patients. In the meantime, efforts should be stepped up to ensure that HIV-infected patients in low-income and middle-income countries who have frequent recurrences of genital herpes or severe genital herpes receive suppressive therapy with aciclovir, as recommended in industrialised countries.[17]

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Identifying sick children in primary care

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In developed countries, every child will present to a primary health-care practitioner more than once every year with symptoms of an acute infection.[1] Primary care physicians faced with such a child know that the likelihood of serious disease is about 1%, but what has not been clear is the evidence-based approach that clinicians should take in investigating such children. In *The Lancet* today, Ann Van den Bruel and colleagues[2] address this uncertainty in a systematic review of 30 studies.

Cyanosis, rapid breathing, poor peripheral perfusion, and petechial rash were confirmed as red flags (ie, warning signs) for serious infection. This finding will come as no surprise to many doctors. In settings with a low prevalence of serious infection, the presence of cyanosis or poor peripheral perfusion raised the probability of severe illness from 1% to between 25% and 30%. Parental concern and clinician's instinct were also identified as strong red flags, but