

recommendations. Because this was a phase 2 trial that was not powered for comparison of regimens, a phase 3 trial is needed to compare the two doses of raltegravir in patients co-infected with HIV and tuberculosis. In the interim, despite findings from the pharmacokinetic study in healthy volunteers showing a reduction in raltegravir trough concentrations with rifampicin,<sup>4</sup> the results of Grinsztejn and colleagues' study are the best clinical outcome data available and lend support to the use of standard doses of raltegravir when given with rifampicin, pending a larger phase 3 trial.

In this trial, the investigators assessed the use of raltegravir with tuberculosis treatment in first-line ART, and the findings might not be applicable to patients on second-line and third-line regimens, in which the importance of raltegravir concentrations in the regimen might differ.

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## Pre-exposure prophylaxis to intensify the fight against HIV

Over 2 million people are newly infected with HIV each year. Nonetheless, there is cause for optimism, because a growing number of evidence-based, efficacious HIV prevention methods are being implemented worldwide, including antiretroviral treatment of HIV-infected people, voluntary medical male circumcision, HIV testing, harm reduction, and behavioural risk reduction. Although new prevention methods such as prophylactic vaccines and topical microbicides are still needed, identification of how to deliver those effective methods we already have is imperative. Pre-exposure prophylaxis (PrEP) with the antiretroviral drug tenofovir disoproxil fumarate alone or in combination with emtricitabine was efficacious for the prevention of HIV acquisition in clinical trials among diverse populations.<sup>1–4</sup> PrEP offers an option to prevent HIV that is under the control of an uninfected person, particularly during times when

other prevention options fail. Optimisation of its use and effectiveness is a priority.<sup>5</sup>

The iPrEx (Pre-Exposure Prophylaxis Initiative) trial<sup>1</sup> showed that PrEP was effective for HIV prevention among men who have sex with men (MSM) and transgender women; in *The Lancet Infectious Diseases*, Susan Buchbinder and colleagues<sup>6</sup> used data from iPrEx to assess two measures of population-level risk—the population-attributable fraction (PAF) and number needed to treat (NNT)—to identify subgroups of MSM and transgender women for whom PrEP would have the greatest benefits. Their work is a clever use of the data from this landmark trial. The principal finding was that MSM and transgender women who practised receptive anal intercourse without a condom in the 3 months before trial enrolment had the ideal combination of a high PAF and a low NNT. This risk factor alone accounted for 64% of new infections in



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this high-risk cohort; treatment of only 36 men with daily PrEP would prevent one new infection each year. Only half of participants in the iPrEx trial adhered to PrEP, but HIV protection was estimated to be over 90% in those who did adhere;<sup>7</sup> thus, in adherent MSM and transgender women, the NNTs are probably even lower than those presented in Buchbinder and colleagues' present study.

HIV risk is heterogeneous, even in high-incidence populations, and a key challenge of HIV prevention in generalised epidemics (or epidemics that are generalised within specific populations, such as MSM and transgender women) is how to prioritise individuals who would benefit most. Risk-scoring methods have been developed to identify individuals with combinations of key risk factors, and more work like this is needed to help prioritise resource delivery.<sup>8,9</sup> Buchbinder and colleagues<sup>6</sup> show that, for at-risk MSM and transgender women like those recruited in iPrEx, one question about recent sexual behaviour—whether or not receptive anal intercourse without a condom had been practised—could open up a conversation about PrEP.

In addition to receptive anal intercourse without a condom, Buchbinder and colleagues<sup>6</sup> identified cocaine use and history of sexually transmitted infections (STIs) as other risk factors with high HIV incidence (9.5 and 4.9 per 100 person-years, respectively), low NNTs (12 and 41), and reasonable PrEP efficacy (87% and 50%); however, they had low PAFs (6% and 9%) because these practices were less common than receptive anal intercourse without a condom. For clinicians caring for MSM and transgender women, these characteristics should signal an unmet prevention need. For public health agencies, which have seen a global resurgence of STIs in MSM and transgender women,<sup>10</sup> rolling out PrEP in MSM and transgender women with substance use or a recent STI, or both, could be a first step to a broad public health effect with PrEP and would benefit those at greatest immediate risk.

A common critique of PrEP has been that its use will lead to increased sexual risk taking. On the contrary, risk behaviours decreased in iPrEx and PrEP trials in heterosexuals, potentially resulting from counselling that accompanied PrEP delivery.<sup>11,12</sup> Indeed, data from the study by Buchbinder and colleagues<sup>6</sup> emphasise that individuals already choosing to have sex without

condoms might benefit most from PrEP. Like in other areas of preventative health care (eg, contraception for women who want to avoid pregnancy), HIV prevention must present options tailored for patients' needs.<sup>13</sup>

In the iPrEx trial, the dominant HIV risk associated with receptive anal intercourse without a condom was with partners of unknown HIV serostatus. There remains a global gap in knowledge of HIV status, and the status of one's partners, and strategies to increase testing and disclosure are essential to combination prevention efforts. Additionally, receptive anal intercourse without a condom with partners with known HIV infection accounted for only a small fraction of new HIV infections, because few men identified known HIV-positive partners. Although heterosexual and MSM HIV-serodiscordant couples are low hanging fruit for PrEP, particularly when the HIV-infected partner delays or declines antiretroviral therapy, these results show that PrEP cannot be solely for identified serodiscordant couples, if there is to be a substantial effect on the HIV epidemic.

More than 3 years after the iPrEx trial showed the efficacy of PrEP,<sup>1</sup> PrEP delivery to MSM and transgender women is being hindered by slow dissemination of these results to at-risk people and hesitancy in provider ownership of this primary prevention intervention. The popular press has begun to push for a place for PrEP as part of HIV prevention.<sup>14</sup> Data like those presented by Buchbinder and colleagues<sup>6</sup> help define how best to use this important new approach to prevent HIV transmission.

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## In for the long haul: 20 years of malaria surveillance

The past 20 years have seen many changes in malaria control. In most countries where malaria is endemic, first-line treatment has switched several times as drug resistance has developed, moving from chloroquine through to artemisinin-based combination therapies. In the past decade, thanks to increased funding through the Global Fund to Fight AIDS, Tuberculosis and Malaria, coverage of long-lasting insecticide-treated nets (LLINs) has massively expanded. These efforts have led to a substantial reduction in the incidence of malaria mortality,<sup>1</sup> with a cumulative total of about 3.3 million deaths prevented since 2001, according to the 2013 World Malaria Report.<sup>2</sup>

In *The Lancet Infectious Diseases*, Jean-François Trape and colleagues<sup>3</sup> describe a remarkable longitudinal study of Dielmo, a village in sub-Saharan Senegal. The epidemiological monitoring in this study was truly exceptional because it was both unusually intense and sustained over long period of time. Over the 22 years of the study, there were more than 2 million person-days of fever surveillance, 92 000 anopheles sampled, and 31 000 blood films examined for parasites.

The resulting dataset describes in great detail the rise and fall of malaria. For example, the entomological inoculation rate (a measure of local transmission intensity) peaked at nearly 500 infective bites per person per year at the height of chloroquine resistance in the year 2000, and decreased to a minimum of 7.6 infective bites per person per year in 2012. Prevalence of *Plasmodium falciparum* dropped from 72% in 1990 to 0.3% in 2012, and the

incidence of clinical malaria fell to 17 cases in 2012, compared with 771 in 2000. The authors conclude that these reductions result from the combination of two factors: the shift away from chloroquine to artemisinin-based combination therapies and the introduction of LLINs.

How do these findings compare with trends in the epidemiology of malaria elsewhere in Africa, and what do they mean for the future? First, this study echoes previous findings of a general decrease in malaria transmission in other African countries, both nearby (The Gambia<sup>4,5</sup>) and further away (Kenya<sup>6</sup>). This similarity helps to confirm that reductions in the clinical outcomes noted at the macro scale in large-scale surveys and from health facility records are also manifested at the village micro level scale.

Second, in several other locations, large decreases in malaria following the scaling up of coverage with LLIN and artemisinin-based combination therapies have been reported,<sup>7,8</sup> but in most cases, these interventions were introduced more or less simultaneously, or shortly after each other, and the relative contributions of the two has been difficult to distinguish. In Dielmo,<sup>3</sup> artemisinin-based combination therapy was used for 5 years before the introduction of LLINs, allowing some separation of the effects of these two interventions. In the absence of LLINs, the artemisinin-based combination therapies produced a large and immediate reduction in the incidence of clinical malaria episodes but had a modest effect on transmission intensity (entomological inoculation



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