towards people most at risk or affected by the virus, but locally available health systems and resources should also be used to capitalise on diverse sources of funds. This approach could enable scale-up of funds to better implement and focus life-saving interventions.

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From Durban to Durban: end of AIDS further than hoped

The International AIDS Conference in July celebrated the success of antiretroviral treatment (ART) in reducing illness and death.[1] The pall of despair that hung over the the previous Durban conference in 2000 has truly lifted, and in one of the great success stories of global health 17 million people have begun ART. Despite this achievement the mood was sombre as the goal of an end to AIDS receded; but it was also purposeful, and we can do much to bring the goal closer.

We commend the UNAIDS 90-90-90 strategy for fostering testing and linkage to treatment and WHO for guidelines to support it.[2,3] However, substantial implementation obstacles exist, the greatest of which is that a large proportion of people living with HIV do not know they are infected. In particular, key populations are less likely to access HIV services because of the stigma and discrimination reinforced by laws that criminalise people who inject drugs, men who have sex with men, and sex workers. Even if expanded testing enables us to achieve the first 90 (assuming we know the correct country denominators) and even if patients are retained and adherent for life (regrettably improbable), the 90-90-90 cascade omits 27% of those with HIV. Transmission dynamics are complex, and the 27% left behind most probably include hard-to-reach, stigmatised populations and people with difficult to detect acute primary infection, who together are responsible for most transmissions. The UNAIDS prevention gap report shows new HIV infections stagnating at 2·1 million annually, with many countries experiencing unexpected increases.[4] IHME's independent estimates are even higher—74 countries with increased HIV incidence and 2·5 million new infections every year.[5] In many countries, including Botswana, South Africa, and Swaziland, HIV incidence remains distressingly high, even as we approach or attain the ambitious 90-90-90 treatment goals. Moreover, in a cluster randomised test and treat trial in KwaZulu-Natal, TasP did not reduce new HIV infections.[6] True that the HPTN 052 results provide incontestable proof of treatment as prevention efficacy among carefully selected stable partners in a meticulously monitored research setting.[7] But we are not yet seeing, nor should we expect to see, comparable population level effectiveness in the real world. Without underestimating the transformative effects of treatment in reducing AIDS morbidity and mortality and slowing HIV transmission, we will not end this epidemic with tablets alone.

The START[8] and Temprano[9] trials finally showed that immediate ART initiation in adults with CD4 counts greater than 500 cells per µL reduces the risk of primary events by 57% compared with deferring ART until CD4 count falls below 350 per µL. The number of deaths, however, was the same in both arms and the absolute difference in the primary clinical endpoint was modest, perhaps because both trials were stopped prematurely.[10,11] On balance, the personal health benefits combined with the public health benefit

of reducing HIV transmission justifies treatment of all irrespective of CD4 count. However, long-term retention and ART adherence present challenges that will increase as an ever growing number of healthy people are identified with little immediate incentive to remain linked to care or to take regular therapy. Drug resistance is growing in many developing countries, reaching 20–40% in many settings, because of late detection of virological failure.[12] Second-line and third-line regimens are too expensive and often unavailable. Moving to immediate treatment will require more resources—an additional US$15 billion may be needed to treat the 15 million people currently not receiving treatment. This expansion threatens to overwhelm fragile health systems, which are also dealing with other health priorities and growing challenges, particularly NCDs. We need to ensure vertical and horizontal equity in terms of support for those with advanced HIV disease and other pressing health needs. Differentiated models of care according to disease stage and client-centred approaches managed by community health workers (CHWs) were high in the Durban agenda. However, the burden of HIV care cannot simply be shifted to CHWs withouth stronger operational research and evidence of the tasks they can and cannot do.

We need to revitalise comprehensive and differentiated prevention, including ART-based prevention for key populations, reinforced by wider education, social protection particularly for women and young girls, and structural interventions led and financed by other sectors. We need to redouble our investment in research and new technologies, including the vaginal ring, long-acting and implantable antiretrovirals, and pre-exposure prophylaxis (PrEP). Evidence of the efficacy of PrEP continues to grow.[13] However, as we embrace its undoubted promise, we must heed the lessons of TasP and resist false blandishments of a new magic bullet. We have never ended a global epidemic without a cure or vaccine, and HIV will not be an exception.[14,15]

Princes, princesses, and celebrities helped to raise the visibility of the conference, but we wish more presidents, prime ministers, senior legislators, and development and finance ministers had attended. International HIV financing is falling, from $8·6 billion in 2014 to $7·5 billion in 2015,[16] and is perilously reliant on one source, the USA, which provides two-thirds of all international financing. Full replenishment of the Global Fund is still at risk, also because global priorities are shifting to other relevant health priorities such as maternal mortality, nutrition, and NCDs, to other important sustainable development goal challenges, such as climate change, but also, unfortunately, to wide global threats, including conflict, migration, and security. For many outside the AIDS movement, the slogan "ending AIDS" meant "AIDS has ended", and we must find new ways of re-engaging heads of government and finance ministries who may not understand the long-term developmental and financial implications of stubbornly high incidence and inexorably rising treatment costs.

We face a long, generational fight. AIDS must become embedded into the wider architecture of development assistance for health. HIV responses should be included in national budgets and national health systems must commit to comprehensive prevention interventions with renewed focus on scaled implementation, grounded in the complexity of HIV transmission dynamics and the inherent messiness of real world operational challenges.[17] Countries need to promote greater domestic financing and to understand the shift from an emergency response to a sustained development response in which HIV is integrated into national plans aimed at universal health coverage and based on rigorous operational research.

Fortunately, the remarkable success of ART continues to buy time to allow the implementation of new comprehensive, scaled prevention and to seek the new scientific approaches needed to end AIDS. We must seize this opportunity with renewed urgency, and with an honest appreciation of the enormity of the ground still uncovered.

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Pharmacology supports on-demand PrEP

Several clinical trials have shown that tenofovir-based oral pre-exposure prophylaxis (PrEP) prevents HIV acquisition from sexual and injection drug-use exposures to the virus. The original PrEP regimen used oral daily dosing regardless of the timing of possible HIV exposures. The rationale for daily dosing is that HIV exposures may be unanticipated or unpredictable and daily dosing ensures continuous therapeutic drug concentrations.

Molina and colleagues[1] reported the results of the placebo-controlled IPERGAY trial in 400 HIV-men who have sex with men (MSM) in France and Canada. IPERGAY evaluated an on-demand PrEP regimen consisting of a loading double tablet dose of tenofovir disoproxil fumarate and emtricitabine 2–24 h before sex, with single tablets at 24 h and 48 h after. The intent-to-treat efficacy was 86% (95% CI 40–98) with 14 infections in the placebo group compared with two in PrEP group, both of which were in patients non-adherent to the regimen by pill counts and drug level testing. Although only a single study, this strong data has led to the regimen's endorsement in France and Canada. Here, we highlight pharmacological evidence that supports the high efficacy of this regimen even for infrequent HIV exposures.

The IPERGAY results are consistent with drug concentration analyses conducted as a part of the iPrEx trial[2] in 2499 MSM and transgender women. iPrEx investigators modelled the gradient in HIV risk reduction associated with tenofovir diphosphate concentrations by comparing HIV seroconverters to HIV-negative controls[3] and estimated the tenofovir diphosphate concentration associated with a 90% reduction in HIV risk (EC_{90}). The iPrEx investigators applied the model to tenofovir diphosphate concentrations in the STRAND study[4] of directly observed dosing in 21 participants taking two, four, and seven tenofovir tablets per week and inferred HIV risk reductions of 76%, 96%, and 99% for these dosing patterns, respectively. Data from the iPrEx OLE[5] and PrEP-DEMO[6] studies in MSM and transgender women supported this; none of the combined 30 HIV seroconversions had tenofovir diphosphate concentrations consistent with four or more pills per week at the time of infection.

Parsing the protection in IPERGAY is complicated by the regimen's frequent use. Participants reported using a median of 15 tablets per month (IQR 9–21), which is nearly four tablets per week. The iPrEx model suggests this dosing pattern alone would be highly protective.

	Proportion with levels above EC_{90}	Estimated HIV risk reduction (95% CI)
One	17%	77% (40–93)
Two	44%	89% (51–98)
Three	71%	96% (60–100)
Four	84%	98% (67–100)
Seven	90%	99% (70–100)

PrEP=pre-exposure prophylaxis with tenofovir disoproxil fumarate with emtricitabine. EC_{90}=drug concentration associated with 90% risk reduction.

Table: **Proportion protected and average efficacy of different pill doses of PrEP for men who have sex with men**