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Closing in on HIV goals

The latest World AIDS Day report from UNAIDS is boldly entitled *Results*, presumably representing an optimistic recognition that tangible and extensive progress is being made. As is pointed out in the foreword by Aung San Suu Kyi and Michel Sidibé in reference to access to treatment, "what had taken a decade before is now being achieved in 24 months". But in addition to optimism, the report is an attempt to sustain momentum as we enter the "final years of working towards the [2015] Millennium Development Goals and the United Nations Political Declaration on HIV/AIDS".

The headline statistic from the report is a greater than 50% drop in new infections with HIV in 25 low-income and middle-income countries between 2001 and 2011. Most of these countries are in sub-Saharan Africa, where most new infections occur. In total this reduction represents 700 000 fewer new infections worldwide in 2011 than in 2001. South Africa (the country with the highest number of people infected with HIV) is not among these countries, although it has achieved a commendable reduction of 41% during the same period. But it is not universally good news—sub-Saharan Africa still accounted for 72% of all new infections with HIV. There were also substantial increases in the numbers of new infections in many countries of Asia, eastern Europe, and Oceania. However, these more negative data are not overlooked in the report; it is acknowledged that this is not a time for complacency, and recognised that the road to zero new infections is a long one.

AIDS-related deaths have also decreased substantially. This success is attributed to "sustained investments in access to antiretroviral therapy by donors and national governments". But the gap between the need for treatment and access is still 46%, and an earlier report from UNAIDS, *Meeting the Investment Challenge*, stated that at present rates of investment there would be an estimated investment gap greater than US$7 billion by 2015. A substantial proportion (48%) of present funding comes from the USA, so its renewed commitment in the form of the *PEPFAR Blueprint* provides some reassurance.

Although funding overall seems good ($16·8 billion at present with an estimated $24 billion needed by 2015), breakdown of the distribution of funding reveals that resources need to be more strategically targeted at key risk groups and key interventions. For example, the prevention of mother-to-child transmission receives $201 million, but $1·1 billion will be needed by 2015. Similarly, investments aimed at effecting behavioural change have received $70 million, substantially less than the estimated $625 million needed.

The targeting of mother-to-child transmission is crucial, particularly because good progress has been made: between 2009 and 2011, half of all new infections with HIV averted were in newborns. It is essential that this momentum is not lost. As the report states, "more effort is needed to ensure that pregnant women tested for HIV during antenatal care are also tested for eligibility for antiretroviral therapy". In addition to maintaining efforts in sub-Saharan Africa where progress has been made, we also need to ensure that such interventions in other regions are brought up to more acceptable levels. Coverage in south and southeast Asia is 18% and in the Middle East and north Africa is 7%. Overall, only 30% of eligible pregnant women with HIV received antiretroviral therapy in 2011. The report calls for qualitative research to establish why pregnant women are not starting treatment despite improvements in access to health care.

Continuing the focused approach to tackling HIV, the populations at highest risk need to be more effectively targeted. Sex workers, men who have sex with men, and injecting drug users are still disproportionately affected by HIV. The poor responses to these groups continues to be the greatest failure in the tackling of HIV/AIDS. The inevitably political reasons behind these failures call into question some of the commitment to genuinely see the back of the disease.

As with many recent reports on HIV, the message is that much has been achieved but there is still much to be done. However, although we must not lose sight of our 2015 target we must also begin to take a longer view and ask ourselves if the political will to tackle HIV will continue beyond this watershed. As we push towards the goals of 2015 we must ensure that the results are tangible and sustained. Nothing would make a greater mockery of the efforts so far than triumphant headlines come 2015, but with waning commitments when the spotlight fades. ■ *The Lancet Infectious Diseases*

For the **UNAIDS World AIDS Day report** see http://www.unaids.org/en/resources/campaigns/20121120_globalreport2012/

For **Meeting the Investment Challenge: Tipping the Dependency Balance** see http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/20120718_investmentchallengesupplement_en.pdf

For the **PEPFAR Blueprint** see http://www.pepfar.gov/documents/organization/201386.pdf

Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

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Summary

Background Intensified antibiotic treatment might improve the outcome of tuberculous meningitis. We assessed pharmacokinetics, safety, and survival benefit of several treatment regimens containing high-dose rifampicin and moxifloxacin in patients with tuberculous meningitis in a hospital setting.

Methods In an open-label, phase 2 trial with a factorial design in one hospital in Indonesia, patients (aged >14 years) with tuberculous meningitis were randomly assigned to receive, according to a computer-generated schedule, first rifampicin standard dose (450 mg, about 10 mg/kg) orally or high dose (600 mg, about 13 mg/kg) intravenously, and second oral moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg once daily. All patients were given standard-dose isoniazid, pyrazinamide, and adjunctive corticosteroids. After 14 days of treatment all patients continued with standard treatment for tuberculosis. Endpoints included pharmacokinetic analyses of the blood and cerebrospinal fluid, adverse events attributable to tuberculosis treatment, and survival. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01158755.

Findings 60 patients were randomly assigned to receive rifampicin standard dose (12 no moxifloxacin, ten moxifloxacin 400 mg, and nine moxifloxacin 800 mg) and high dose (ten no moxifloxacin, nine moxifloxacin 400 mg, and ten moxifloxacin 800 mg). A 33% higher dose of rifampicin, intravenously, led to a three times higher geometric mean area under the time-concentration curve up to 6 h after dose (AUC_{0-6}; 78·7 mg.h/L [95% CI 71·0–87·3] *vs* 26·0 mg.h/L [19·0–35·6]), maximum plasma concentrations (C_{max}; 22·1 mg/L [19·9–24·6] *vs* 6·3 mg/L [4·9–8·3]), and concentrations in cerebrospinal fluid (0·60 mg/L [0·46–0·78] *vs* 0·21 mg/L [0·16–0·27]). Doubling the dose of moxifloxacin resulted in a proportional increase in plasma AUC_{0-6} (31·5 mg.h/L [24·1–41·1] *vs* 15·1 mg.h/L [12·8–17·7]), C_{max} (7·4 mg/L [5·6–9·6] *vs* 3·9 mg/L [3·2–4·8]), and drug concentrations in the cerebrospinal fluid (2·43 mg/L [1·81–3·27] *vs* 1·52 mg/L [1·28–1·82]). Intensified treatment did not result in increased toxicity. 6 month mortality was substantially lower in patients given high-dose rifampicin intravenously (ten [35%] *vs* 20 [65%]), which could not be explained by HIV status or severity of disease at the time of presentation (adjusted HR 0·42; 95% CI 0·20–0·91; p=0·03).

Interpretation These data suggest that treatment containing a higher dose of rifampicin and standard-dose or high-dose moxifloxacin during the first 2 weeks is safe in patients with tuberculous meningitis, and that high-dose intravenous rifampicin could be associated with a survival benefit in patients with severe disease.

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Introduction

Meningitis is the most severe form of tuberculosis, resulting in death or neurological disability in 50% of patients.[1,2] The treatment in patients with tuberculous meningitis follows the model for short-course chemotherapy in patients with pulmonary tuberculosis, but the optimum drug regimen and duration have not been established.

Rifampicin is important in the treatment of tuberculous meningitis as shown by the high mortality in patients with rifampicin-resistant tuberculous meningitis.[3,4] However, the dose used is at the low end of the dose-response curve,[5,6] and the penetration of rifampicin into cerebrospinal fluid is low.[7] Higher doses of rifampicin for pulmonary tuberculosis have been assessed in several clinical trials reported before 1985.[8,9] Until now, no data were available for the use of high-dose rifampicin in tuberculous meningitis, although one clinical trial is underway in Vietnam.[10] Apart from a higher dose of rifampicin, intravenous rather than oral administration might improve the drug penetration into the plasma and cerebrospinal fluid.

Penetration of other standard drugs for tuberculosis, isoniazid and pyrazinamide, into the cerebrospinal fluid is good and they are important for treatment of tuberculous meningitis. By contrast, neither ethambutol nor streptomycin, both commonly used drugs, show good penetration into the cerebrospinal fluid in the