RUNNING IN PLACE:

TOO MANY PATIENTS STILL IN URGENT NEED OF HIV/AIDS TREATMENT

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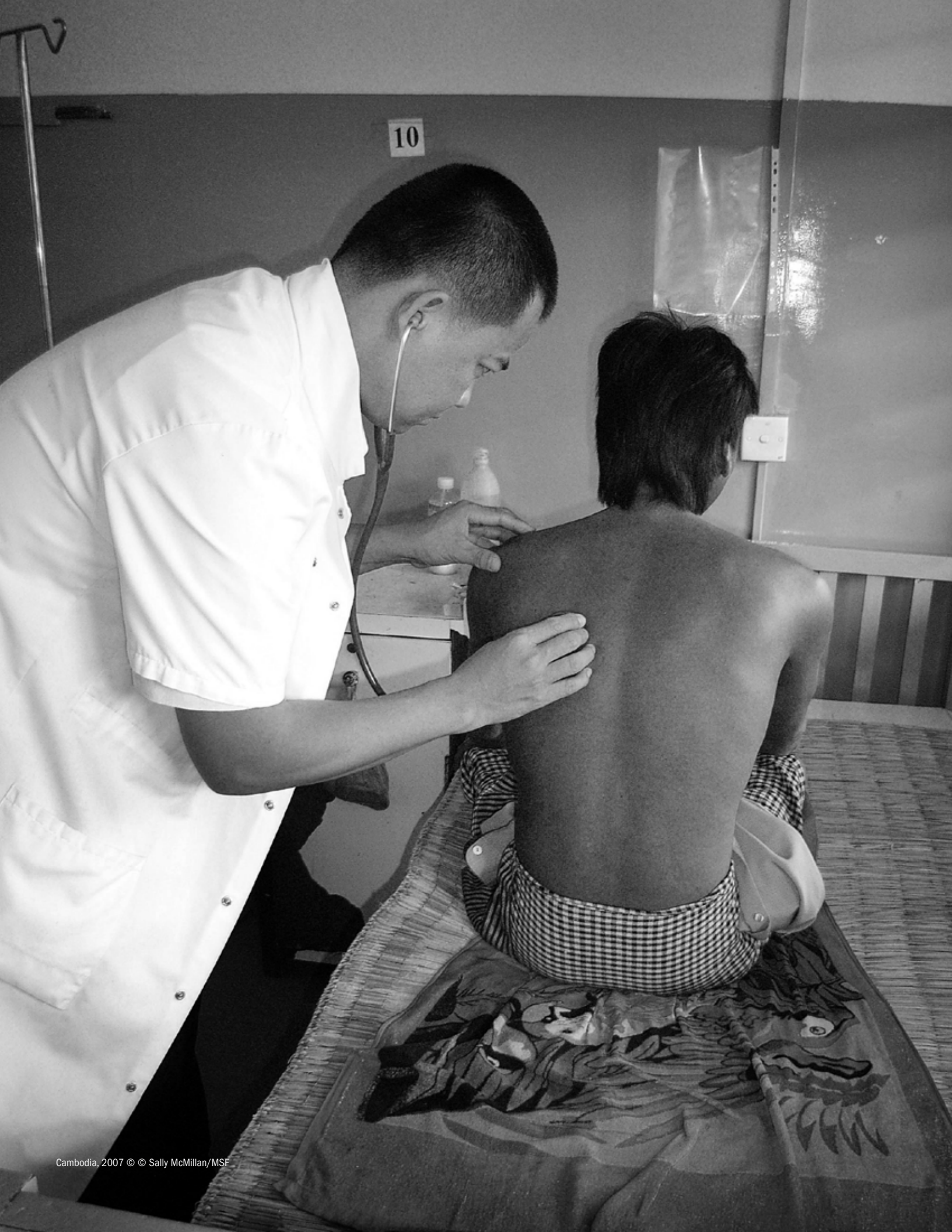

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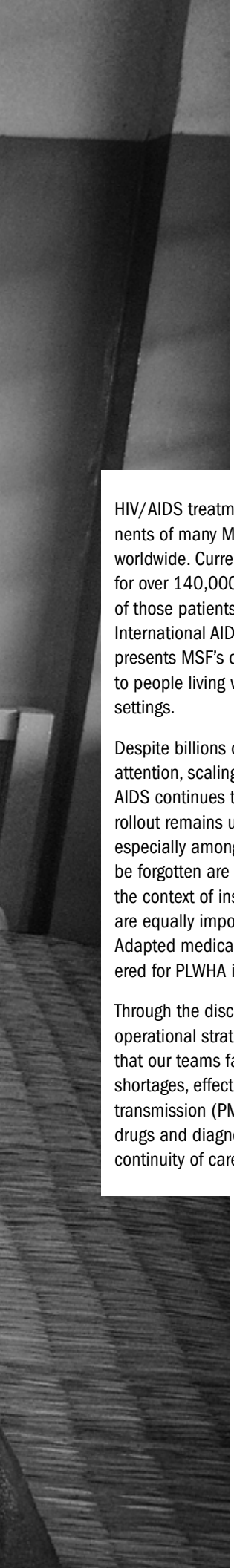

HIV/AIDS treatment and management are essential components of many Médecins Sans Frontières (MSF) programs worldwide. Currently MSF provides antiretroviral therapy (ART) for over 140,000 patients in 27 countries, with about 10,000 of those patients being children. In conjunction with this year's International AIDS Conference in Mexico City, this document presents MSF's current "state of play" in providing quality care to people living with HIV/AIDS (PLWHA) in resource-limited settings.

Despite billions of dollars in funding and widespread global attention, scaling up effective medical care for people with HIV/AIDS continues to pose massive challenges. Progress in ART rollout remains uneven, with major deficits in certain countries, especially among vulnerable groups and in rural areas. Not to be forgotten are conflict-affected areas of the world, where in the context of instability and insecurity the needs for HIV care are equally important but less well understood as elsewhere. Adapted medical and operational strategies must be considered for PLWHA in these zones.

Through the discussion of MSF field activities, experiences, and operational strategies, we highlight the critical HIV/AIDS issues that our teams face today, which include health care worker shortages, effective pediatric care, prevention of mother-to-child transmission (PMTCT), HIV-TB co-infection, access to needed drugs and diagnostics, and program indicators of quality and continuity of care.

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Mind the gaps: HIV/AIDS treatment in times of healthcare worker shortages

An estimated 70% of people living with HIV/AIDS (PLWHA) who need ART are still not receiving it. As the numbers of patients started on ART increase worldwide, the human resources for health (HRH) needed to manage and maintain care are lagging far behind. In countries where ARV drugs are now available, the acute shortage of health staff is one of the main reasons for failing to reach more patients. In contrast with public announcements from governments and international agencies, effective immediate measures on the ground are still missing.

Whereas the World Health Organization (WHO) minimum standard for the number of doctors per 100,000 people is 20, countries like Malawi, Mozambique, and Lesotho have ratios of 2, 3, and 5, respectively, based on 2006-2007 population and health data. Similarly, the WHO minimum standard for nurses per 100,000 people is 100, but the ratios in the same three countries are 56, 20, and 63, respectively.[1]

Every day, MSF teams witness how the critical shortage of healthcare workers impacts the lives—and untimely deaths—of people with HIV/AIDS. We see patients forced to wait months to start treatment while their health deteriorates. For example, in two MSF-supported programs in Angonia and Mavalane districts in Mozambique, before important changes in patient flow and capacity, median waiting times for ART were 42 and 54 days, respectively, for patients enrolled in 2006. Rates of pre-ART loss to follow-up were 69% and 87%, respectively. Also, long waiting times for consultations increase the risk of patients interrupting treatment. Overwhelmed clinicians are thus under immense time pressures and do not have the time to perform thorough assessments of patients on treatment, which risks missing out on crucial signs of complications and/or health deterioration.

One primary strategy used by MSF and others is task shifting, combined with other measures to deliver care.[2] Task shifting refers to a change in task allocation between different types of professional health workers (mostly lower cadres), or from professional to lay workers. It is a common practice for general health care both in developed and developing countries. In sub-Saharan Africa, especially rural areas, special cadres of non-physician health workers have been created to perform clinical tasks where physicians are scarce.[3]

MSF regularly utilizes task shifting in its ART programs where physicians or other medical staff are in short supply. In a review of 19 MSF projects, task-shifting activities in HIV/AIDS care were assessed, looking at care setting, task division, staff qualifications, and workload management.[4] The review showed that task shifting was mainly used in response to countrywide shortages of qualified health workers, particularly in southern African nations. Clinics in sub-Saharan Africa were either overloaded, centralized hospital-based ART programs, or ART care decentralized to health centers mainly in rural areas with extremely limited health staff. Clinical tasks were shifted to non-physician clinicians and nurses. Lay workers mainly performed tasks for HIV testing and counseling, adherence counseling, treatment literacy, and social and educational support. Lay workers were a valuable additional workforce within the health facilities, stepping in to perform registrations, simple patient assessments, and drug dispensing and explanations. Supervision was crucial to quality of care, requiring support from qualified staff.

An example of ART scale-up and rollout in the face of severe HRH shortages, albeit requiring additional financial and human resources, is MSF's experience in Thyolo, Malawi. Thyolo district is a poor, rural region of Malawi, where MSF has one of its largest cohorts of patients on ART at well over 10,000, with about 450 new patients started on ART each month. Starting in 2005, the central hospital became overwhelmed by the increase in new patients. Patient time was severely constrained, and many patients had difficulties reaching the hospital for treatment, due to distance and cost of transport. Over the following years, ART initiation and follow-up were decentralized to 14 health centers

[1] Help Wanted. Confronting the health care worker crisis to expand access to HIV/AIDS treatment: MSF experience in southern Africa. MSF, May 2007.
[2] Philips M, Zachariah R, Venis S. Task shifting for antiretroviral treatment delivery in sub-Saharan Africa: not a panacea. Lancet 2008;371:682-4.
[3] Mullan F, Frehywot S. Non-physician clinicians in 47 sub-Saharan African countries. Lancet 2007;370:2080-1.
[4] Philips M, Wouters A, Arnould L, Rasschaert F. Inventory of task shifting practices in ART care projects supported by Médecins Sans Frontières (MSF) [abstract]. IAC 2008, Mexico City.

Malawi, 2006 © Julie Remy

(7 of which do initiations). Both within the ART clinic in the hospital and in the health centers, task shifting was implemented. Clinical officers, medical assistants, and nurses were trained and supported to handle ART initiation and follow-up. Additional workforce was summoned through nurses, lay workers, and community volunteers (often PLWHA) to administer testing, counseling, and psychosocial and nutritional support. In addition to the task shifting, extra clinical staff were recruited, treatments reorganized, and incentives provided.

In a 2007 analysis of the Thyolo program, 91% of patients (enrolled June 2006-December 2007) were still alive and on ARVs, illustrating the effectiveness of this decentralized, task-shifting treatment strategy, despite the relative difficulty and complexity of its implementation and costs.[5] Further comparative analysis of retention and attrition rates (June 2006-June 2007) showed that of 4,074 patients followed up for a total of 1,803 person-years, >80% were still retained in care at both the hospital and health centers. Retention at the health centers was significantly higher than at the hospital level (adjusted hazard ratio: 1.2, $P<0.001$). Attrition rates (death, lost to follow-up, ART stoppage) were similar at approximately 15%. Similarly, in a MSF treatment program in Lusikisiki, South Africa (handed over in 2006), task shifting and health center-based care resulted in >80% of patients still alive and on ART after 1 year.

In MSF's program in Lesotho, ministry of health (MOH) nurses at one district hospital and 14 rural health centers initiate and monitor patients on ART, and are supported by MSF mobile medical teams who visit each clinic weekly to provide clinical mentorship and other support. Facility-based lay counselors have become central to comprehensive patient management, performing a wide range of tasks including HIV testing and counseling, ART preparation, adherence support for both ART and TB treatment, scheduling of appointments, and identification and tracing of defaulters. At the most overloaded facilities, a simplified screening tool is being piloted where certain senior counselors can provide drug refills for stable adult patients (defined as non-pregnant adults on ART >12 months with no new opportunistic infections, ARV side effects, or adherence problems) and refer patients to nurses at the first sign of any complication. The essential tasks performed by lay counselors help to reduce the workload of nurses so that the nurses can continue to initiate new patients and focus on more complex clinical problems. In this program, 87% of ART patients analyzed were alive and remaining in care at 12 months.

In Tete province, Mozambique, the transfer of counseling tasks from nurses to lay workers allowed MSF to significantly increase the number of patients enrolled on ART. With lay counselors on

[5] Massaquoi M, Gomani P, Nalikungwi R, Bemelmans M, Zachariah R, Philips M. Task-shifting and decentralisation of HIV/AIDS care in a rural district of Malawi: some successes and lessons learnt from Thyolo district [abstract]. IAC 2008, Mexico City. WEAB0202

the team, new ART initiations increased to an average of 16 per month (January-May), compared with 6 per month in the previous period. Adherence rates remained favorable at 8% loss to follow-up, with the lay counselors also tasked with tracing these patients.

The favorable capabilities of lower cadres of health workers are further exemplified by MSF's largest ART program, in Chiradzulu, Malawi, where >12,000 patients are on treatment. MSF in collaboration with the MOH developed a task-shifting strategy transferring ART initiation from clinical officers to nurses and medical assistants in rural health centers. In a May-December 2007 analysis of >1,600 adult patients started on ART, 25% were initiated by nurses and medical assistants.[6] Comparing patients followed by nurses/medical assistants or by clinical officers, 88% and 87%, respectively, were still active at >3 months. No significant difference was observed between outcomes of patients initiated by either group. These nurses and medical assistants trained in ART care thus appeared capable of treating and following up patients comparably with clinical officers in our setup with a simplified protocol.

Despite these local successes, task shifting is not a panacea and has its limits. Even when using qualified health staff more efficiently, MSF and others continue to hit the wall of the HRH shortage, especially as it pertains to significant ART scale-up. To effectively counter the HRH crisis, task shifting must be part of a larger strategy of retention and training of health care workers. Urgent mobilization at multiple policy levels is needed to sustain health workers in caring for their patients. Measures must be taken by donor, national, and international entities to retain skilled health care workforces and to attract new staff by increasing salaries and improving working and living conditions, as well as providing access to treatment and health care for the workers themselves.

International "brain drain" has also contributed to the HRH crisis, as workers leave poorer countries for better salaries and working conditions in richer countries. But such brain drain is also common within regions themselves. Countries like South Africa attract doctors and nurses from countries with lower remuneration, such as Democratic Republic of Congo, Lesotho, Malawi, Nigeria, and Zimbabwe. Codes of conduct and similar initiatives try to curb unethical international recruitment. Despite such pull factors, with necessary support and remuneration, more health staff may prefer to remain in their home countries.

In addition to salary and working conditions, illness and death among health staff add to continued loss. In Lesotho, Malawi, and Mozambique, death is the leading cause of health worker attrition, with a significant proportion being HIV-related. To keep health workers alive and active is a crucial challenge in countries with high HIV prevalence and staff loss. Paradoxically, health professionals face stigma and difficulty accessing

[6] McGuire M, Goossens S, Kukasha W, et al. Nurses and medical assistants taking charge: task-shifting HIV care and HAART initiation in resource-constrained and rural Malawi [abstract]. IAC 2008, Mexico City. WEPE0106

Malawi, 2006 © Julie Remy

HIV/AIDS treatment. Availability of confidential HIV testing, care, and treatment services for health workers is therefore of utmost importance. At the local level, several initiatives have been taken to improve access to care for HIV-infected staff. In Thyolo, Malawi, MSF supported the district health authorities in setting up a specialized clinic for staff and their immediate family members, as well as a staff support group. This initiative increased the number of health staff on ART from 31 to 58 over 2 years.

Although the scale and scope of the health worker crisis is now well acknowledged, effective interventions are still limited or slow to be implemented. Policymakers in national, donor, and international agencies have expressed their concern and pledged support. The Global Fund has adapted funding modalities to include health systems strengthening, with specific calls for proposals, in rounds 8 (July 2008) and 9 (October 2008), for measures to boost the health workforce by improving remuneration and increasing recruitment. Still to be seen are the actual scope and size of these proposed funding opportunities.

As these long-term solutions continue to be discussed, clinic staff, district health authorities, and nongovernmental organizations cope daily with the gaps but barely manage to keep clinics running. The main challenge is how to bring ART to patients in rural and difficult-to-access areas, where the demanding work and difficult living conditions make it problematic to attract and keep health care staff. Without short-term, emergency measures to boost and retain staff, the nurses and other health workers present in the field are likely to leave on short notice, ultimately causing health services to collapse and leaving too many HIV patients untreated.

PRIORITIES

Urgent and crucial steps to plug the gaps in health workforce include:

- Greater flexibilities in national work policies and scope of practice to allow task shifting to lower-qualified medical and non-medical workers
- Improved access to treatment for workers who themselves may become sick
- Training and recruiting additional qualified staff
- Increased salaries and benefits for national health workers involved in clinical care
- Improved work and living conditions for staff, particularly in rural areas
- Revision of multilateral and bilateral donor rules and practices allowing increased financial support to boost the public health workforce
- Lifting of salary and workforce spending limits by national and international finance bodies

Pediatric care and prevention of mother-to-child transmission (PMTCT): Establishing standards of care

Pediatrics

The treatment of children and adolescents is an essential part of HIV/AIDS care. MSF currently treats over 10,000 pediatric patients (<15 years of age) with ART in over 50 projects worldwide. These programs are situated in resource-poor settings and face complex challenges for effective pediatric HIV management.

Over the last 5 years throughout MSF, nearly 4,000 children <5 years of age have been started on ART in 48 programs in 20 countries. About 90% of these children are in Africa, with 10% in Asia and <1% in Latin America. An analysis of all children (<5 years old) started on ART from April 2002 to January 2008 in these MSF programs showed that 79% were still on treatment. Survival of children <12 months of age was found to be significantly lower compared with older age groups. Overall, ART in young children appears effective and well-tolerated within MSF programs, but comparatively poor survival in the youngest children suggests the need for earlier access to infants at risk.

In two MSF programs in Cambodia, a high early mortality rate (death within first 6 months after enrollment) was observed among children, with the rate 8-fold higher among those not yet started on ART compared with those placed on treatment.[7] In a program in Homa Bay, Kenya, data analysis by Epicentre showed that survival in children (n=34) after 3 years of ART was similar to that reported elsewhere in adults.[8] Despite this positive result, viral suppression was found to be absent in 50% of treated children.

Such results point to the need for adapted pediatric ARV formulations and child- and context-appropriate adherence strategies.

Of the ARVs available in pediatric formulations, most are ill-adapted for use in resource-limited settings. The drugs exist either as powders needing to be mixed with water, or as syrups often requiring refrigeration and having a bitter taste. One positive development was the approval in August 2007 of pediatric-formulation fixed-dose combination (FDC) tablets for 3TC/d4T/NVP (Baby and Junior Triomune). Still, pediatric formulations for safer and newer ARVs are needed.

MSF's largest cohort of pediatric patients on ART is in Bulawayo, Zimbabwe, where in conjunction with the MOH, provision of highly active antiretroviral therapy (HAART) for children was started in 2004. In Bulawayo, >1,400 pediatric patients are currently on ART. Substantial gains in CD4 cell counts have been seen in these pediatric patients at 6 and 12 months of ART (range 45-180%). After 4 years, pediatric clinical outcomes included a 6.3% mortality rate, 7.9% lost to follow-up, and 1.7% treatment failure (based on virological assessment).[9] This program exemplifies the feasibility of scaling up pediatric HIV care in a setting with low resources and high prevalence.

Positive outcomes have also been seen in a nurse-based pediatric HIV program in two MSF-supported health centers in Kigali, Rwanda. In an analysis from late 2003 to mid 2007, a total of 315 children (<15 years old) started on ART. Median follow-up time after ART start was 2 years, and 84% of the children were still on treatment. Important features of the program included the availability of viral load testing (87% tested), adequate training and supervision of the ARV-administering nurses, and family-centered care with psychosocial and educational support for the children. The favorable patient results of this program demonstrate the feasibility and effectiveness of decentralized pediatric HIV care in a resource-limited setting.

Pediatric diagnostics also play a crucial role in HIV care since early initiation of ART in children reduces mortality. The WHO recently revised its pediatric guidelines to test infants at

[7] Raguenaud M-E, Isaakidis P, Te V, Seitaboth S, Akao K, Zachariah R. Early mortality (pre and post antiretroviral treatment) amongst children with HIV/AIDS enrolled in two programmes in Cambodia [abstract]. IAC 2008, Mexico City. THPE0101

[8] Sauvageot D, Knight L, Otieno M, et al. Good immune restitution but unsatisfactory viral suppression in children on ART in a remote Western Kenyan area [abstract]. IAC 2008, Mexico City. MOPE0213

[9] Parreño F, Nyathy M, Palma PP, Roddy P, Alonso E. Analysis of clinical and immunological outcomes of an HIV positive paediatric cohort treated at Mpilo Hospital in Bulawayo, Zimbabwe [abstract]. IAC 2008, Mexico City. LBPE1155

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4-6 weeks using DNA-based diagnostics (and to start all HIV-positive infants <12 months old on ART regardless of clinical or immunological stage). Despite such proactive strides for earlier treatment of children, implementation is a challenge because, for many national programs, the polymerase chain reaction (PCR) equipment required for DNA testing is expensive, requires trained personnel, and is logistically demanding.

Proper counseling and education for children living with HIV/AIDS, such as appropriately disclosing HIV status or making medical information understandable, are often insufficient in resource-poor settings. Children are often treated like small adults or, worse, excluded, where counseling is addressed only to the caregivers and not the children. To address this, MSF projects, such as those in Kompong Cham and Phnom Penh, Cambodia; Busia and Kibera, Kenya; Chiradzulu and Thyolo, Malawi; Arua, Uganda; and Bulawayo and Tsholotsho, Zimbabwe, have developed family and group-counseling education programs for children and their parents. These programs provide information in books, films, toys, and play sessions on how HIV attacks the body, how ARVs work against the virus, and why blood draws and CD4 cell counts are important. MSF has begun to look at the concept of a basic minimal support package for pediatric HIV patients, ie, a minimal set of specific measures for patient support, including health education, treatment literacy, ARV preparation, individual and group counseling, children's "clubs", and social support.

PMTCT

HIV-positive children largely become infected from their mothers, either during pregnancy, delivery, or the breastfeeding period. In developed countries, pediatric HIV infection has been nearly eliminated through successful prevention of mother-to-child transmission (PMTCT). Transmission rates in developed countries are typically below 2%.[10,11] However, in developing countries, PMTCT interventions have not been as successful, with an estimated 420,000 new pediatric (<15 years old) infections globally in 2007.[12] In the US, fewer than 250 infected infants are born each year according to current estimates.[13] Today nearly 90% of all HIV-positive children live in sub-Saharan Africa.

Treatment providers, including MSF, continue to struggle to prevent newborn infections, grappling with complex protocols and high numbers lost to follow-up.[14] PMTCT is an increasingly important component of MSF's projects, and from our field experience the need for simplified protocols is clear. MSF currently offers PMTCT interventions in 54 projects, with >10,000

[10] Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS 2008;22:289-99.

[11] Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. AIDS 2008;22:973-81.

[12] AIDS Epidemic Update. UNAIDS, Geneva, December 2007.

[13] Centers for Disease Control and Prevention (CDC), Mofenson LM, Taylor AW, et al. Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. MMWR Morb Mortal Wkly Rep 2006;55:592-7.

women having started in a PMTCT intervention in 2007. Major emphasis is placed on integrating PMTCT into routine antenatal care (ANC) and maternal and child health (MCH) services, such as in Arua, Uganda; Chiradzulu and Thyolo, Malawi; and Nairobi (Mathare and Kibera), Homa Bay, and Busia, Kenya; as well as in Lesotho, Burkina Faso, and Liberia. Collection and analysis of data in MSF's PMTCT programs are in the early stages.

In many developing countries, women have little access to ANC. All mothers should be informed of the need for HIV testing, so that if positive they can receive both treatment for themselves and interventions for preventing HIV transmission to their children. Today only an estimated 20% of HIV-positive pregnant women are receiving ARVs for PMTCT.[15] Although reasons for this low coverage rate include financial barriers, human resource shortages, and weak health systems for MCH, one neglected but crucial factor is that of the protocols and formulations available. The protocols are complicated, and adapted ARV packaging, such as single-dose nevirapine (NVP) syrup or zidovudine (AZT) syrup for one week, are unavailable.

Also, protocols applied to developing countries differ from those used in developed countries. In developed countries, any pregnant woman who is HIV-positive has the option to receive full ART throughout pregnancy, followed by formula feeding for the infant. In most resource-limited contexts, this is not an option. To protect infants from infection, interventions are being explored to simplify the PMTCT protocol in resource-limited settings, including HAART for all HIV-positive women throughout pregnancy and the breastfeeding period. Preliminary studies under trial environments have shown some success, with HIV transmission rates as low as nearly 1%.[16] Access to triple therapy for all pregnant women regardless of immunological status (CD4 count) has been shown to be the best way to prevent HIV transmission to the child. MSF is currently looking at implementing triple therapy in the last trimester of pregnancy and throughout breastfeeding in some pilot projects. Discussions continue on how best to approach the breastfeeding period.

Rolling out and implementing PMTCT interventions on a large scale would require the identification of the most appropriate ARV combination and the development of an adaptable FDC that is easy to administer, has favorable toxicity, and has minimal risk of resistance. Some national frameworks have already adapted simplified protocols for their PMTCT programs, and international and national guidelines should be adapted to reflect these realities. The need is evident for the international community to expediently examine new strategies for implementing simplified PMTCT protocols in resource-limited settings, all so that child HIV infections can be significantly reduced.

PRIORITIES

Optimizing pediatric HIV care in resource-limited settings requires:

- Earlier and improved access to at-risk infants, with active follow-up of PMTCT-born newborns and testing of enrolled patients' children
- Integration of PMTCT into MCH services, including antenatal and postnatal care
- In high prevalence contexts, the offer of early infant diagnosis at vaccination sites
- Pediatric and PMTCT FDC drug regimens
- Reliable, easy-to-use, inexpensive, point-of-care diagnostic tools adapted for pediatric use, and routine diagnostic facilities in high-risk populations, such as malnourished children
- Proper management of opportunistic infections, such as TB in pediatric cohorts
- Improvement of adherence through patient and peer-support measures for both mothers and their children, including support tools according to age group

[14] Bwirire LD, Fitzgerald M, Zachariah Z, et al. Reasons for loss to follow-up among mothers registered in a prevention-of-mother-to-child transmission program in rural Malawi. Trans R Soc Trop Med Hyg 2008. Published online ahead of print 16 May 2008.
[15] Unite for Children. UNICEF, 2007.
[16] Arendt V, Ndimubanzi P, Vyankandondera J, et al. AMATA study: effectiveness of antiretroviral therapy in breastfeeding mothers to prevent post-natal vertical transmission in Rwanda [abstract]. 4th International AIDS Society Conference, July 22-25, 2007; Sydney, Australia. TUAX102

Cambodia, 2007 © Dieter Telemans

HIV-TB co-infection: Integrated programs, comprehensive care

Tuberculosis (TB) accelerates the progression of HIV-related immune suppression and is one of the leading causes of death among PLWHA. Diagnosis of TB in HIV-positive individuals is difficult, often leading to delays in treatment, which in turn contributes to increased death rates. Nearly a quarter of a million PLWHA died of TB in 2006. People living with HIV/AIDS are up to 50 times more likely to develop active TB in a given year compared with HIV-negative individuals[17] and roughly a third of the 33 million PLWHA worldwide are infected with latent TB. In the past 15 years, new TB cases have tripled in countries with high HIV prevalence, but <1% of PLWHA were screened for TB in 2006.[18]

Increases in multidrug-resistant (MDR) and extensively drug-resistant (XDR) cases of TB add another dimension of complexity to the diagnosis and treatment of HIV-TB co-infection. In HIV/AIDS patients co-infected with XDR-TB, case fatality rates surpass 90%.[18]

Despite the recognized need for combined care of HIV and TB, the drugs and diagnostics currently available are not appropriate for managing co-infection. Drug interactions when treating both diseases make managing co-infection difficult. Rifampicin, one of the key drugs in TB treatment, can reduce the levels of

[17] Frequently asked questions about TB and HIV. WHO. Available at: http://www.who.int/tb/hiv/faq/en/
[18] Facts on HIV-TB. HIV-TB Global Leaders Forum, 9 June 2008. Stop TB Partnership.

ARVs in the blood. For the most commonly used FDC of 3TC/d4T/NVP, interactions with rifampicin result in lower than acceptable levels of NVP, making a change in ARVs necessary. Efavirenz (EFV) does not share this degree of drug interaction and can be used as an alternative, but this EFV-based combination is not available in a FDC, resulting in patients having to take a more complicated cocktail of medications. This is further complicated if the patient is a young child since no dosage guidelines for EFV are available for children under 3 years of age.

HIV-TB co-infection thus poses a vital challenge for MSF. In response, MSF has reorganized certain of its HIV and TB programs, combining treatment and integrating care for both diseases. MSF runs or has operated integrated HIV-TB programs in several countries, including Cambodia, China, Kenya, Lesotho, Malawi, Myanmar (Burma), South Africa, Uganda, and Zambia.

In the MSF-supported program in Khayelitsha, South Africa, a comprehensive model of care for HIV-TB has been in place since 2003, through a collaboration between MSF and the provincial and city departments of health. Through June 2008, over 9,000 patients are on ART, and the HIV-TB co-infection rate is 70%. Over 150 MDR- and XDR-TB cases were detected in 2005-2006. In December 2007, MSF and the city health department launched a pilot project for community-based management of drug-resistant TB, taking advantage of existing resources and networks previously developed for the community-based ART program.

In Homa Bay, Kenya, MSF, in collaboration with the national TB program (NTP), merged the HIV and TB treatment clinics in 2006. After implementing this joint treatment program, 80% of the TB patients were tested for HIV, and 88% (313/354) were found to be positive for HIV. At the end of TB treatment, 40% of patients were also on ART, with 57% cured or completed treatment, 13% dead, and 12% defaulted.

In Nanning, China, MSF has provided ART since December 2003, and over 700 patients are currently on ART. Approximately 10% of the HIV-infected patients in this program develop active TB each year. Of these TB infections, less than a quarter are easily diagnosed with the most commonly used TB diagnostic test, sputum smear microscopy. Furthermore, less than half are successfully diagnosed after a significant delay because their initial sputum tests are negative.

PRIORITIES

Increasing and improving care for HIV-TB co-infection requires:

- Integrated, comprehensive care services, with combined diagnosis and treatment
- More sensitive diagnostic tools, capable of detecting active TB in HIV-positive patients
- Patient access to simpler combinations of newer AIDS drugs compatible with TB drugs
- Appropriate management of MDR- and XDR-TB, which will require the development of more effective diagnostic and therapeutic tools and novel treatment strategies

South Africa, 2005 © Mariella Furrer

Access to newer and adapted medicines: The challenge remains

HIV/AIDS is a chronic disease requiring lifelong treatment with different ARV combinations for people who develop drug resistance and side effects over time. In MSF's longest-running ART program, in Khayelitsha, South Africa, approximately 22% of patients on treatment for 5 years needed to be switched to a second-line drug combination due to resistance.[19] In MSF's HIV project in Kigali, Rwanda, 16.6% of patients needed to switch to an alternative regimen (median ART duration, 1.5 years) due to side effects related to stavudine (d4T), one of the ARVs most commonly used in first-line drug combinations in developing countries.[20] A further study of a South African cohort found that within 3 years on ART, 21% of patients who had started a d4T-based regimen needed to be switched because of toxicity.[21] In 2006, WHO recommended a move away from d4T to less toxic combinations based on either AZT or tenofovir (TDF).[22] This recommendation however has significant pricing implications.

[19] Untangling the Web of ARV Price Reductions, 11th edition. MSF, July 2008.

[20] van Griensven J, Rasschaert F, Atté EF, Asiimwe A, Zachariah R, Reid T. Toxicity of stavudine- and nevirapine-containing antiretroviral treatment regimens: incidence and risk factors after three years in a large cohort in Rwanda [abstract]. IAC 2008, Mexico City. THPE0188

[21] Boulle A, Orrell C, Kaplan R, et al. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. Antivir Ther 2007;12:753-60.

[22] Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2006 revision. WHO.

High prices for newer ARVs

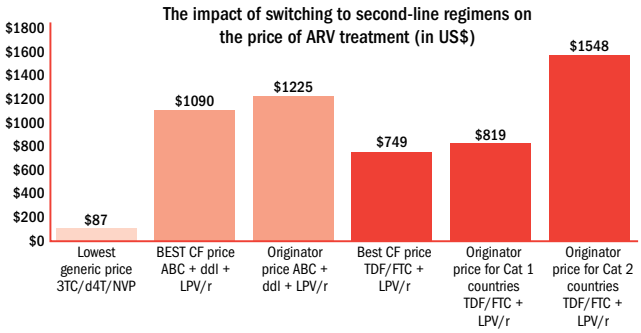
The need for access to less toxic first-line ARV combinations and for options when resistance develops is urgent,[23] yet high prices caused primarily by monopoly control remain a critical barrier. Because of increased global patenting as a result of World Trade Organization (WTO) rules in key generics-producing countries such as India, Brazil, and Thailand, prices are not likely to drop as dramatically as the 99% reduction seen for today's most commonly used first-line ARV regimen, from >$10,000 per patient per year in 2000 to $87 today. National treatment programs will be faced with uncomfortable choices about whether to treat a greater number of patients on more affordable ARV combinations, or fewer patients on less toxic but more expensive combinations.

For example, changing a patient's regimen from the most commonly used d4T-based first-line ARV combination to a less toxic option involves, at best, almost doubling the cost, if substituting with AZT. Switching to a TDF-based regimen would require a price increase ranging from 4- to 11-fold. A model applied to MSF's ART project in Epworth, Zimbabwe estimates that replacing d4T with a TDF-based regimen for all patients from 2008 to 2014 (based on today's prices) would increase ART costs from $2 million to $8.5 million.[24] However, the situation may not be as grim as these numbers suggest, since the study did not take into account reductions in overall costs linked to TDF usage, such as reduced requirements for biological monitoring or management of d4T toxicities, as well as the fact that TDF prices have decreased and will continue to drop as increased quantities of the drug are used.

In a study of the cost-effectiveness of switching from d4T to TDF in South Africa, savings on d4T toxicity management were estimated to offset about 20% of the cost of TDF, based on a price of $17/month (the current lowest price in the public sector).[25] The analysis found that changing to TDF would be highly cost-effective if the price were lowered to about $13/month, and would be cost-neutral for the government at $6/month.

According to estimates, switching a patient who has developed drug resistance from d4T-based first-line ARV combination to a new second-line regimen involves at least a 9-fold cost increase. In some middle-income countries not able to access generic products, up to a 17-fold cost increase would be seen over the most affordable first-line combination (Figure 1).[26]

Figure 1



Keeping the door open for affordable ARVs

Because countries with manufacturing capacity such as India, Brazil, and Thailand did not begin granting pharmaceutical patents until recently, multiple producers were able to compete for the market, which helped bring prices down dramatically. Indeed, India has been called the "pharmacy of the developing world," and MSF sources >80% of its ARVs from India. The lack of patents on individual ARV compounds also allowed for the development of FDCs, which represent an innovation that has simplified HIV/AIDS treatment and helped facilitate global treatment scale-up.

However, newer medicines are likely to be patented in these countries, preventing the competition that leads to lower prices. This means the battle for access to newer drugs will have to be fought in different ways. Public health safeguards enshrined in the WTO TRIPS (Trade-related Aspects of Intellectual Property Rights) Agreement allow countries to overcome patent barriers by issuing compulsory licenses (CLs) to open the market to competition despite a patent. CLs issued by Thailand and Brazil since January 2007 have had a major savings impact on national HIV treatment programs. In Brazil, a CL issued for EFV brought the price down by nearly 70%, from $576 to $190 per year, leading to savings of $30 million from March to December 2007 alone, and a further projected savings of $237 million by 2012.[26] Similarly, a CL issued by Thailand for lopinavir/ritonavir brought the drug price down by 55-75% in middle-income countries.

Further TRIPS safeguards allow countries to design patent laws that limit the scope of patents in the interest of public health. India's Patents Act of 2005, for example, has strict criteria as to which innovations deserve patents and includes a provision allowing any interested party to oppose a patent. Civil society and others have filed multiple oppositions against ARV patents,

[23] Pujades-Rodríguez M, O'Brien D, Humblet P, Calmy A. Second-line antiretroviral therapy in resource-limited settings: the experience of Médecins Sans Frontières. AIDS 2008;22:1305-12.

[24] Kivela J, O'Brien D, Mills C, Sabapathy K. The price of change - replacing stavudine with tenofovir in first-line ART in scaling-up settings [abstract]. IAC 2008, Mexico City. THAD0106

[25] Rosen S, Long L, Fox M, Sanne I. Cost and cost-effectiveness of switching from stavudine to tenofovir in first-line antiretroviral regimens in South Africa. J Acquir Immune Defic Syndr 2008;48:334-44.

[26] Untangling the Web of ARV Price Reductions, 11th edition. MSF, July 2008.

and in June 2008 for the first time such an opposition was successful, when the Indian patent office rejected a patent for the pediatric syrup formulation of NVP.

Diving into the patent pool

The July 2008 decision by UNITAID to in principle establish a patent pool is a groundbreaking development, which may hold the key for access to affordable newer ARVs in the future.[27] MSF, together with Essential Inventions, originally proposed the patent pool concept to the UNITAID board in June 2006, in response to difficulties in accessing newer ARVs. A patent pool is a mechanism whereby a number of patents held by different entities, such as companies, universities, or research institutes, are made available to others for production or further development. The patent holders receive royalties paid by those who use the patents. The pool manages the licenses, patent negotiations, and royalty payments.

A patent pool could facilitate, for example, the development of pediatric formulations or much-needed FDCs for less toxic first- and second-line treatments. Patents on individual compounds typically stand in the way of producing FDCs, a barrier that a patent pool would help circumvent. A patent pool can also help speed up the availability of generic versions of new medicines, because the development can start well before the 20-year patent term expires. At the same time, it will help to increase the size of the potential market because companies that produce drugs under license from the patent pool will be able to export them to any of the countries designated by the pool's licenses.

Critical to a patent pool's success, however, is the patent holders' willingness to include their patent rights in the pool. UNITAID is setting up a task force to design their proposed patent pool. The recently adopted WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property also recommends exploring the feasibility of patent pools.

Newest ARVs need to be adapted for resource-poor settings and pediatric patients

Therapeutic advances for HIV have been seen over the last 2 years, with the approval of new drugs from older classes, as well as entirely new classes. However, these new ARVs are targeted primarily for developed-country markets and have not yet been studied to meet the specific needs of populations in resource-poor countries, where 90% of HIV-positive people live[28] Essential data are lacking for target populations in developing countries, such as pregnant women or patients who also take TB drugs. A further example is the lack of knowledge about drug interactions between antimalarials and ARVs; 80% of HIV-positive individuals live in malaria-endemic regions.[29]

Furthermore, the specific ARV needs of children with HIV must be urgently met. Of the 22 ARVs approved by the US Food and Drug Administration (FDA) for adults, 8 are not approved for use in children, and 9 do not have any pediatric formulations.[30] Although one new drug (tipranavir) was approved in late June 2008 for use in patients 2-18 years old, most of the recently approved ARVs, some with entirely new mechanisms of action (maraviroc, etravirine, darunavir), lack safety and efficacy data for children. This situation exists despite the fact that the FDA has included obligations and incentives encouraging submission of data for pediatric use since 1997, and the European Agency for the Evaluation of Medicinal Products (EMEA) followed suit in January 2007. EFV was approved by the FDA for use in adults in 1998, but dosing for children under 3 years of age has not yet been established.

Generic manufacturers have been at the forefront of developing adapted pediatric formulations, and today several pediatric FDC tablets are finally available, though more are still needed. In countries with the manufacturing capacity, the lack of patents on individual compounds has facilitated the development of these FDCs. Nevertheless, the fact that the first WHO-prequalified pediatric FDC became available a full 6 years after the adult equivalent is distressing. This lag highlights the urgent need to systematically include pediatric studies in the ARV development process, and to ensure that formulations adapted for children are developed at the same time as those for adults.

PRIORITIES

Access to newer, safer, better adapted, and cheaper ARVs requires:

- Price reductions for less toxic first-line ARV combinations (TDF- and AZT-based)
- Development of affordable, adaptable options for adults and children when resistance develops to first-line regimens
- Support for countries' use of TRIPS safeguards such as compulsory licenses and the creation of pro-public health patent laws
- Establishment of a patent pool to foster competition and facilitate the development of needed FDCs for adults and children
- Development and adaptation of HIV drugs and diagnostics for resource-limited settings
- Systematic inclusion of pediatric studies in the development of ARV formulations

[27] UNITAID moves towards a patent pool for medicines [press release]. UNITAID, Geneva, 9 July 2008.
[28] van Roey J, von Schoen-Angerer T, Ford N, Calmy A. How developing world concerns need to be part of drug development plans: a case study of four emerging antiretrovirals. Drug Discov Today 2008;13:601-5.
[29] Malaria and HIV/AIDS. WHO. Available at: http://www.who.int/malaria/malariandhivaids.html
[30] Untangling the Web of ARV Price Reductions, 11th edition. MSF, July 2008.

Quality-of-care indicators and analysis: Scaling up beyond the numbers

Currently, pronouncements on the progress and success in ART implementation have largely been confined to total numbers of patients started on therapy, but the benefits of ART are best realized when patients remain under long-term and uninterrupted treatment. MSF has integrated treatment literacy; adherence counseling; patient and outcome tracking; stockout prevention; decentralization and task-shifting; free health care; and treatment simplification to enhance ART programs and thus the likelihood of patients remaining on long-term ART.

Between 2002 and the end of 2007, the number of people accessing ART is reported to have increased 10-fold, to 3 million individuals in middle- and low-income countries, representing about 30% of those medically in need.[31] In 2006, participating countries in the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS agreed to the principle of "Universal Access" to ART, where by 2010 such therapy is to be available to at least 80% of those in need, representing a greater than 3-fold increase above current coverage.

The budget for national ART programs in these countries has come primarily from external funding sources such as the Global Fund, PEPFAR, and World Bank, though each national program has developed its own strategies for implementation. Although most national programs have many features in common (eg, use of a public health approach, indicators of when to start ART and with which drugs, decentralization of treatment sites to the periphery, task-shifting to non-physician cadres), sufficient differences exist in approach and country capacity in achieving stated program goals that measures of program effectiveness will vary significantly.

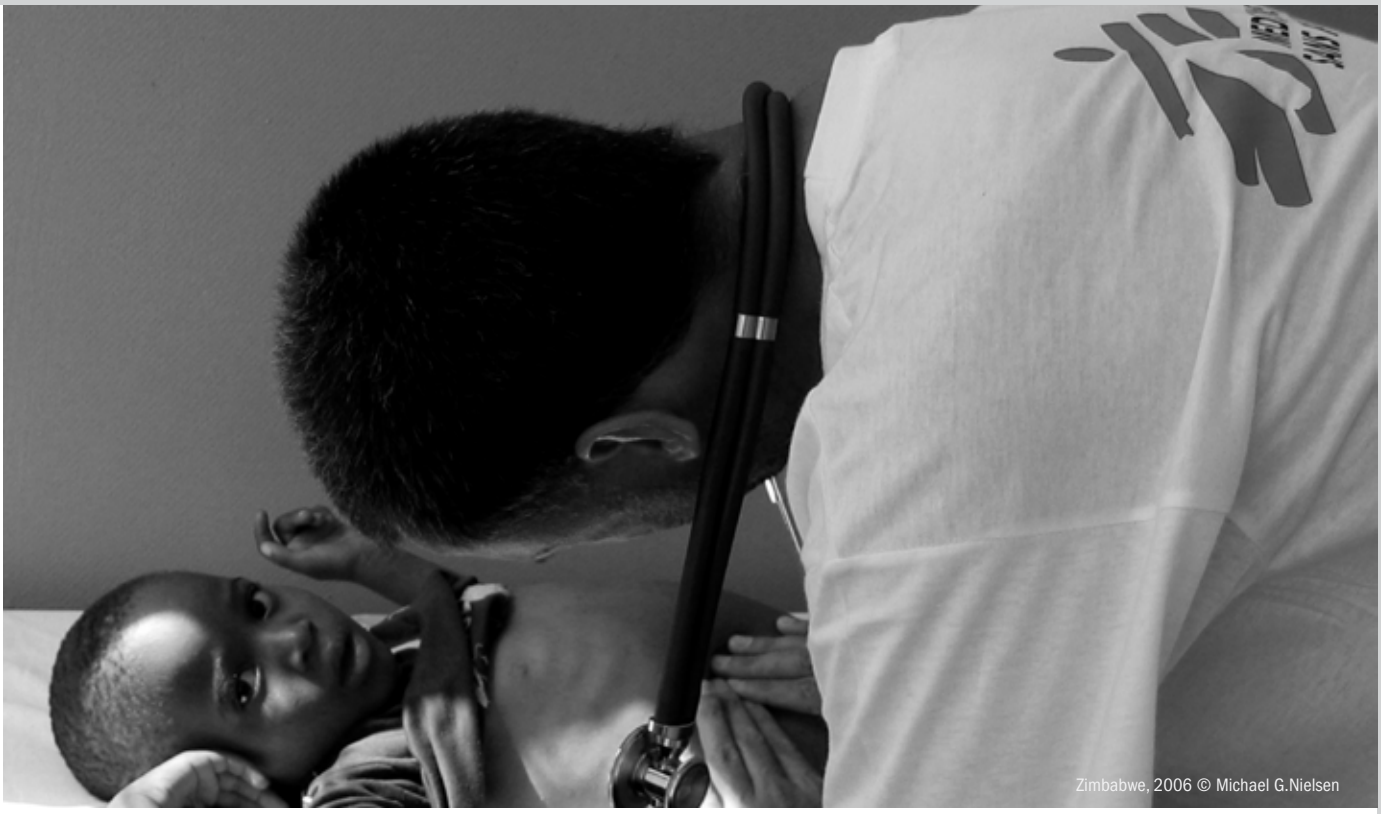
Funding entities (such as the Global Fund through "performance-based" funding, and PEPFAR) and international health agencies (such as WHO and UNAIDS) have provided guidance to implementing agencies, including national programs. To varying degrees, they require reporting on certain pertinent program "quality" indicators. Countries are also encouraged to fund and develop their monitoring and evaluation (M&E) activities. Nevertheless, a deficit of data exists regarding the progress in scaling up beyond the total numbers of patients having accessed treatment.

Clearly systems providing HIV care require the capacity to identify people who have HIV infection, clinical and/or biological markers indicating the need for ART, and when to start them on treatment. In recent years, countries have become increasingly reliable in reporting the total number of patients started on treatment, as well as the proportion of those in need who are receiving it. However, with few exceptions, no comprehensive country data are available on how well national programs are faring in patient retention on ART.

Keeping patients under ART places broader and perhaps more exacting demands on nascent national HIV care programs, compared with the already difficult task of identifying individual patients needing ART. Thus, incorporating quality indicators into ART programs would provide measurable parameters for the effectiveness of these projects and help optimize health outcomes. Simplified, systematic, and standardized means of assessing ART programs using core indicators beyond total number of patients started on therapy should be agreed upon, including survival, retention, frequency and extent of treatment interruption (particularly as related to pharmacy stockouts), adherence, and some measure of adequate human resources (eg, number of full-time equivalent ART provider-days per 1,000 ART patients in a given catchment area). These indicators can drive methodical efforts to improve the quality of care in donor-funded scale-up of ART programs.

In implementing HIV care and ART delivery, MSF directly experiences the difficulties in providing chronic treatment to often very sick patients, and strives, not always with immediate success, to adjust strategies over time to provide quality care. In referral areas to our programs where national efforts are ongoing to scale-up and decentralize ART services, MSF has also witnessed the problematic issues affecting continuity and quality of care in some donor-supported clinics. In some cases, MSF is asked

[31] Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector. Progress report, June 2008. WHO.



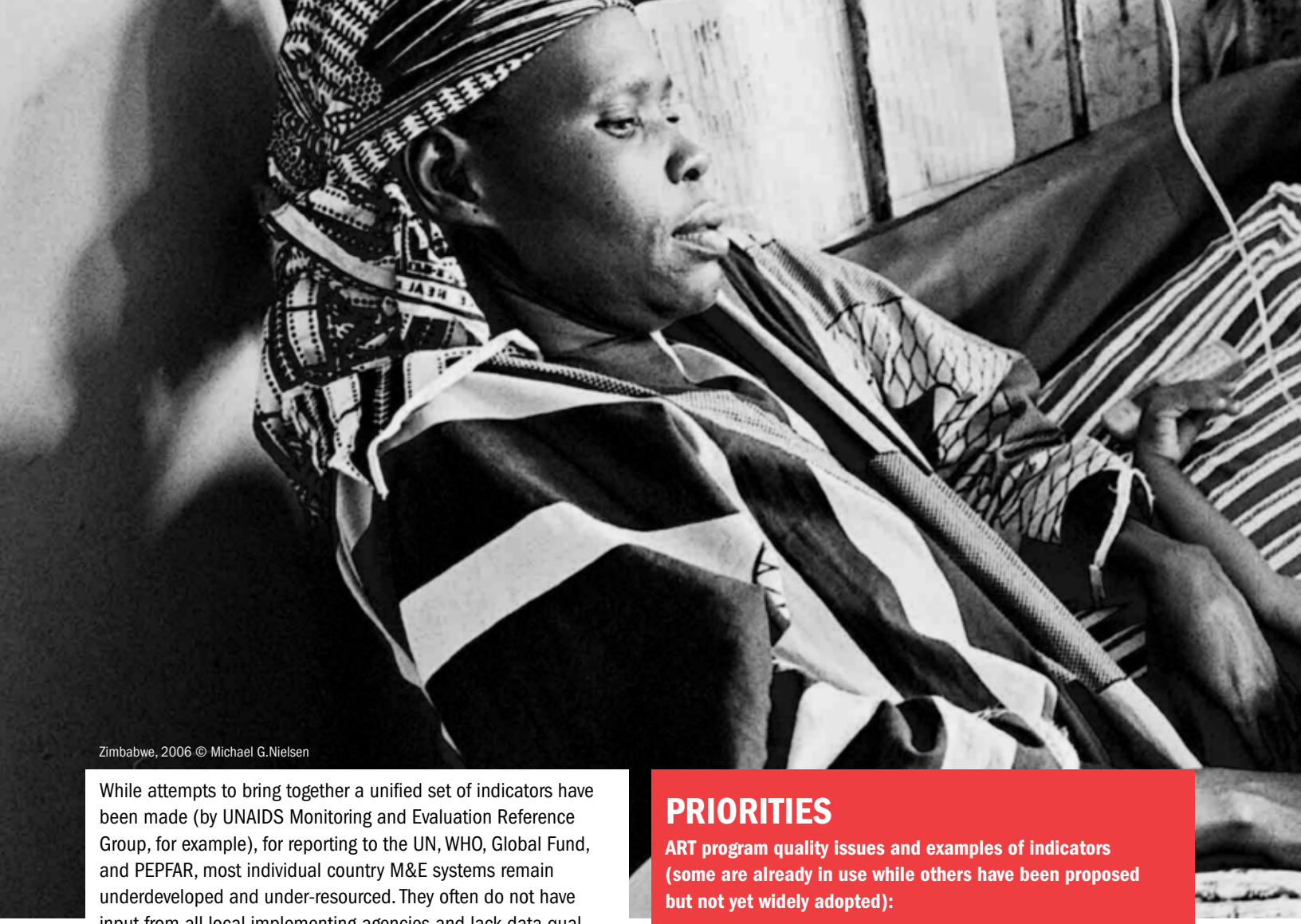
Zimbabwe, 2006 © Michael G.Nielsen

to step in to avoid treatment interruptions or program slowdown. For example, in Uganda at the Arua Regional Referral Hospital, MSF currently treats >4,500 patients with ART in a program started in 2002. MSF began supporting peripheral health centers accredited by the national program to provide ART, so as to help increase access to treatment within the region and to ease overcrowding in the Arua clinic, which currently cares for >7,000 HIV-positive patients. The MSF team was frequently required to refill MOH ARV stockouts due to health center ARV orders not placed or done so too late, inadequate health center pharmacy management, delays in national pharmacy ARV delivery, national pharmacy stockouts, and logistical difficulties in transport (eg, no truck, no fuel).

MSF staff also needed to coordinate drug order transmissions to the central supply managers, give direct patient care in place of absent or overworked health staff, provide supplemental training, and transport patient blood samples to the regional hospital for CD4 testing to avoid patients having to bear the cost and time of traveling to the regional hospital laboratory. In addition, only one clinic had adequately collected data to measure patient retention, with mortality and loss to follow-up at 12 months of 19% and 8%, respectively. The combined proportion of patient loss (27%) for this 12-month period (April 2006-April 2007) was similar to the 30% growth of the overall cohort in the subsequent 12 months (May 2007-May 2008).

In two MSF HIV clinics in Mozambique (Maputo and Lichinga), >5,000 patients are on ART. MSF is in the process of referring these patients from central sites to regional MOH clinics, which receive funding from the Global Fund and PEPFAR. MSF's decentralization teams provide supervision of MOH staff at these clinics, but several barriers to uninterrupted and quality care are present. Large gaps in HRH cause delays in putting severely ill patients rapidly on treatment, and waiting times discourage regular clinic visits. Recurrent and prolonged drug stockouts are observed for ARVs and OI drugs, where MSF is often asked to supply buffer stocks of drugs. This example shows how such clinics are working hard to provide good care but continue to require further support and resources. Monitoring of certain indicators of patient treatment, retention, and outcomes is thus crucial, both to ensure quality care and to intervene when an indicator worsens.

MSF's experience illustrates the emerging challenge of quality and continuity in the provision of care for the 3 million people started on ART in lower- and middle-income contexts. Increases in the numbers of patients on ART and clinics providing HIV/AIDS care may hide important programmatic and support deficits like the ones described here. This highlights the importance of balancing the strategies of scale-up/decentralization and the reality in the field.



Zimbabwe, 2006 © Michael G.Nielsen

While attempts to bring together a unified set of indicators have been made (by UNAIDS Monitoring and Evaluation Reference Group, for example), for reporting to the UN, WHO, Global Fund, and PEPFAR, most individual country M&E systems remain underdeveloped and under-resourced. They often do not have input from all local implementing agencies and lack data quality assurance tools and oversight. Governments, multilateral agencies, and funders should make a concerted effort to define and incorporate a simplified framework of ART program quality indicators that are easy to collect for systematic analysis. This analysis should then be used to address any program deficiencies in strategy or resourcing in a timely fashion, to better ensure that scale-up means not only starting patients on ART but keeping them on it.

PRIORITIES

ART program quality issues and examples of indicators (some are already in use while others have been proposed but not yet widely adopted):

Patient access

- Estimates of ART coverage: proportion actively on ART (not only "ever started") of those in need (by age group and gender)
- Retention in pre-ART care: proportions of mortality and loss to follow-up over time (eg, 12, 24, 36 months) by year of HIV program entry

Program effectiveness

- Proportion/number of patients continuing to receive ART by age group over time (eg, 12, 24, 36 months) by year of ART initiation
- Program attrition rates (mortality, loss of follow-up) using standardized outcome definitions (eg, such as those used by DOTS TB programs)

Program support

- Proportion of clinics with pharmacy stockouts of ARVs and key OI drugs >1 week per annum
- Adequacy of available ART care providers and clinic consultation days (such as number of ART health providers per 1,000 patients on ART and/or mean number of patient consultations per provider per day)

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