



chapter five

sharing**research & knowledge**

Harnessing the power of research to achieve treatment targets and to build health systems that respond to the broad array of complex health issues requires an innovative approach to gathering and sharing information. Existing, classic methods of research and dissemination of new knowledge – while still necessary – will not be sufficient to achieve these goals. In the short term, new methods of assessing the performance of treatment programmes are essential. So, too, is the rapid sharing of information in order for countries to benefit from the most recent and most relevant experience elsewhere and adapt it to local circumstances.

The HIV/AIDS treatment initiative is generating many urgent new research questions for which answers must be found quickly and communicated without delay. The fast progress that is simultaneously occurring in information and knowledge technologies will help. Innovative routes are already beginning to overtake and bypass standard research publishing processes and other conventional forms of knowledge sharing.

Traditional notions of research and publication are insufficient to bridge the wide gap between current knowledge and its successful application. A new approach is required which recognizes that useful knowledge can expand beyond formal research designs and can be quickly shared and applied through social networks and other channels, rather than simply through traditional publication methods. These applications of knowledge management in the public health sector are

relatively new, but early efforts show promise (1).

A modern approach to knowledge management strengthens existing information and research networks through the Internet and other means of communication, and builds vibrant new networks that allow the rapid sharing of knowledge and practical experience at the front line – among clinicians, researchers, health workers and others. Thus, the people most closely involved in achieving wider access to antiretroviral therapy can learn from each other's successes – and also from their failures – especially if this takes place in an atmosphere of transparency.

Both successes and failures have characterized much of the history of HIV/AIDS research in all its forms. Since

scientists first identified the human immunodeficiency virus (HIV) as the cause of AIDS in 1983, many remarkable research achievements, spanning the understanding, treatment and prevention of the disease, have benefited many millions of people. Twenty years ago no effective treatment was known; today a range of antiretroviral drugs exists – treatments that dramatically improve patients' quality and length of life, though they are still reaching only a tiny fraction of those who need them. Meanwhile, despite high hopes 20 years ago for an HIV vaccine, the world is still waiting. Notwithstanding significant advances, it will be several years at least before a safe and effective vaccine becomes widely available.

The development, licensing and delivery of such a vaccine remains the greatest hope for the eventual control of HIV/AIDS, and realizing this hope depends on scientific research. In examining the continuing quest for a vaccine, this chapter reviews research into other important areas of HIV/AIDS prevention, treatment and care. Even while awaiting effective vaccines, the moral obligation is unambiguous: to scale up activities to treat and care for people living with HIV/AIDS – whoever they are and wherever they live – and to contain the spread of the disease. Such ethically sound actions require new tools that can be produced only by research of the highest quality, research which must extend far beyond the laboratory to include multidisciplinary operational and health policy research.

HIV/AIDS researchers face four broad categories of challenge, all crucial to present and future success:

- Prevention research – slowing down the growth and geographical expansion of the epidemic: a challenge for epidemiology and sociobehavioural aspects of prevention.
- Vaccine research – designing a safe and effective preventive vaccine: the best hope for the long-term prevention and control of HIV/AIDS.
- Treatment research – generating new antiretroviral drugs and designing new therapeutic strategies that would be active on “wild” and resistant strains of viruses, be easy to take and better tolerated than currently available drugs: a challenge for basic and clinical research.
- Delivery system research (operational research) – making care and antiretroviral treatment available to all those who need it worldwide: a multidisciplinary undertaking. This is the greatest research challenge because it must deliver results on the ground, often more complicated than the relatively straightforward task of scientific discovery. Furthermore, this aspect of research has, until now, been largely neglected by both researchers and funding organizations. Here, too, a knowledge management framework may prove useful.

PREVENTION RESEARCH

Linking prevention and access to treatment

As efforts to provide treatment are scaled up, concerns have been voiced regarding its potential impact on preventive behaviours. The availability of treatment, some fear, may lower people's perception of risk and hence lead to lower vigilance; in contrast, others argue that the strengthening of health-related interventions will encourage testing and counselling, and that the knowledge of HIV status may increase protective behaviour. Studies of people living with HIV in developing countries indicate that treatment is, indeed, associated with increased sexual activity but, at the same time, it is associated with more consistent condom use. In developed countries, an increase in risky behaviour was documented among certain population groups after the

introduction of effective antiretroviral therapy, without clear evidence of why this happens (2, 3). The epidemiological data are only suggestive, and trends need to be documented across settings, over time, and among key subpopulations, in particular in people living with HIV/AIDS and other highly exposed groups.

Treatment may directly contribute to prevention of new infections to the extent that lowering of viral load decreases the probability of sexual transmission. Decreased infectiousness is likely to be counterbalanced by increases in the life expectancy of patients. Research must contribute to the adaptation of interventions in order to ensure the sustainability of prevention over the long term (4, 5).

More generally, better evidence is needed on how preventive behaviours can be promoted across age groups, sexes, social strata and different categories of serological status, especially in the context of scaling up access to treatment. The mechanisms linking risk perceptions to behavioural change are shaped by contextual variables and are situation-specific and partner-specific (6). Better evidence is also needed on the extent to which the findings from developed countries are valid for developing countries. There are also indications that gender influences the selection of strategies to reduce risk (7). It is important to investigate whether such differences in perceived risks and protection represent a general gendered pattern.

Treatment and care for children with HIV



Young HIV-positive children at the Incarnation Children's Center, New York, USA, play with their carers. The Center is funded to conduct clinical trials of new treatment options, including antiretroviral therapy.

Many children with HIV have lost a parent to the disease. They are likely to have behavioural and emotional difficulties, which can complicate their treatment as they grow older.

Microlevel studies indicate that medical information and public health recommendations are not automatically accepted by the general public and that people interpret professional advice in the light of local notions and past experience with health care (8). Investigations of beliefs and practices that are contrary to public health recommendations can suggest ways to communicate better with the public. The availability of effective treatments should contribute to furthering confidence in medicine and public health.

Preventing transmission from mother to child

Among the issues that urgently require further research are better methods of ensuring the prevention of HIV transmission from mother to child, particularly in developing countries and in the postnatal period. Every year, an estimated 700 000 children become infected with HIV. The overwhelming majority acquire the virus through mother-to-child transmission, which can occur either during pregnancy and delivery or postnatally during breastfeeding. In the absence of any intervention, rates of this form of transmission can vary from 15% to 30% without breastfeeding, and reach as high as 45% with prolonged breastfeeding (9). Transmission during the peripartum period accounts for one-third to two-thirds of overall numbers infected, depending on whether breastfeeding transmission occurs or not, and this period has therefore become a focus of prevention efforts.

Transmission of HIV from mother to child can be prevented almost entirely by anti-retroviral drug prophylaxis (usually now given in combinations), elective caesarean section before onset of labour and rupture of membranes, and refraining from breastfeeding (10, 11). In resource-poor countries, however, elective caesarean section is not a safe option, and refraining from breastfeeding is often not feasible or acceptable. In Africa, no more than 5% of HIV-infected women and neonates who could benefit from interventions are receiving them.

Antiretrovirals, either alone or in combinations of two or three drugs, have been shown to be highly effective in reducing mother-to-child transmission of HIV. Evidence of the efficacy of antiretroviral prophylaxis from Africa, Europe, Thailand and the USA has been demonstrated for short-course drug regimens. The substantial efficacy of triple combinations has been shown in observational studies in industrialized countries (10, 11), where rates of transmission are now below 2% in the absence of breastfeeding. There is an urgent need for evidence from breastfeeding mothers in sub-Saharan Africa, one of the most affected populations. Short-term safety and tolerance of the prophylactic regimens have been demonstrated in all the controlled clinical trials on mother-to-child transmission (12). Further studies of these issues are required, especially on the long-term implications of potential antiretroviral resistance for HIV-infected mothers and their children.

Preventive interventions with antiretrovirals have not yet been successfully implemented on the scale required (13). Even where antiretroviral treatment is applied peripartum, infants remain at substantial risk of acquiring infection in the breastfeeding period. These facts also require investigation; they demonstrate once again the need to strengthen health systems, while integrating HIV/AIDS interventions with reproductive and maternal and child health services.

Protecting women with microbicides

Protecting women against HIV infection is another important area for researchers. Microbicides are anti-infective products such as gels, creams, impregnated sponges and similar devices that women apply before sexual intercourse to prevent HIV transmission and other sexual infections. Unlike the condom, their use is controlled by the woman and they will not necessarily be contraceptive. Attempts are also being made to incorporate microbicides into silicone intravaginal rings that are left in the vagina for several weeks to ensure contraception, with sustained release of the agent providing continuous protection against infection.

Microbicides could make a very substantial difference by widening people's choice of protective interventions. To achieve high levels of use will require a continuing education process aimed at women as well as health policy officials and providers. Epidemiological modelling based on data from over 70 low-income countries suggests that even a partially effective microbicide is likely to have a significant impact on the epidemic: a product that is only 60% effective in protecting against HIV could avert 2.5 million new infections over a three-year period, even if it is used in only 50% of sex acts not protected by condoms, and assuming it is used by only 20% of people easily reached by existing health services (14). However, the microbicide concept has only recently received sufficient support to allow progress to be made. Pharmaceutical companies have not so far regarded microbicides as providing economic incentives for substantial investment, though the Bill and Melinda Gates Foundation is now giving serious consideration to this matter.

VACCINE RESEARCH

Although advances have been made in both prevention and treatment, the best hope for prevention and control of HIV/AIDS lies in the development, licensing and delivery of a safe and effective preventive vaccine.

The existence of globally diverse strains of HIV remains one of the greatest obstacles to HIV vaccine development. Attempts to design immunogens capable of eliciting effective neutralizing antibodies against those strains have been unsuccessful. In the absence of such immunogens, the main focus has been on developing vaccines to elicit cell-mediated immunity against HIV. This type of vaccine could suppress viral load, slow the progression of disease, and potentially blunt transmission (15).

The design of improved next-generation candidate HIV vaccines faces many scientific challenges. The mechanisms for protective immunity are unknown, as are the necessary antigens. Despite the failure of one of the most hopeful candidates in recent efficacy trials, however, it is now clear that circulating HIV strains can in fact be neutralized. Another challenge is the extensive genetic diversity of HIV, suggesting that successful vaccines may need to contain cocktails of antigens from across different clades of the virus. Recent clinical data on some vaccines currently in clinical trials have been encouraging, but whether the responses elicited by the vaccines correlate with clinical protection awaits human efficacy trials.

The development of an HIV vaccine faces hurdles of manufacturing, clinical trials, regulation and delivery. These aspects will need to be tackled to ensure that safe and effective HIV vaccines are licensed and delivered as quickly as possible. The development of vaccines is hampered by the limited capacity for efficacy trials, particularly in

the developing world. There is also limited regulatory capacity to facilitate the testing and eventual licensure of successfully developed HIV vaccines.

The next five years will probably see the first results from efficacy trials testing the concept of vaccines that aim to suppress viral load, slow disease and potentially blunt transmission of HIV. Several new candidates are expected to be evaluated in clinical trials for safety and immunogenicity. It is likely, however, that to achieve significant improvements in HIV vaccine design and improve the prospects for success, solutions to the major scientific questions will need to be found. As a result, the major stakeholders in HIV vaccine development have recently come together to propose a “global enterprise” to accelerate HIV vaccine development (16). Achievement of this vision will probably require significantly greater resources. The International AIDS Vaccine Initiative recently found that worldwide expenditure for research on HIV vaccines was, in 2001, between US\$ 500 million and US\$ 600 million, which represented only 10% of the expenditure for research in other areas of HIV/AIDS. Creative strategies to enhance coordination and collaboration among the many stakeholders are also required.

TREATMENT RESEARCH

A cornerstone of efforts to reach universal access targets is sustained dedication to basic research and to the understanding of AIDS pathogenesis, in order for new drugs, novel therapeutic strategies and vaccines to be designed and developed.

The availability of potent combinations of antiretroviral drugs in the developed world has resulted in a steep decline in HIV-associated morbidity and mortality. Death rates from AIDS fell by 80% over the four years following the launch of highly active antiretroviral therapies in Europe and North America. Following their more widespread introduction in the second half of the 1990s, it also became clear that issues relating to adherence, toxicities, immunological and virological failure of treatment, and occurrence of resistance all needed to be tackled.

Sustaining long-term adherence

Effective treatment with antiretroviral drugs requires long-term adherence. From an operational research point of view, monitoring the uptake of treatment involves: defining optimal measures of adherence which can be used in resource-poor countries; assessing the validity of self-reports, compared with other methods such as pharmacy records or electronic monitoring systems; and identifying ways to encourage more accurate reporting by patients.

Evidence shows that the variables with the strongest effect on adherence are treatment-related. These include the complexity of the regimen, side-effects, the “battle fatigue” that results from long-term use, and patients’ attempts to remedy these problems by modifying the dosage or administration of drugs. Misperceptions and lack of trust regarding the medication’s effectiveness further compound these problems. Women face unique obstacles related to child care, lack of partner support, and the attitudes of peers and family members. Among the social variables that are found to affect adherence, stigma and fear of disclosure have the strongest effects (17). In addition, costs matter: copayment is detrimental to long-term adherence (18).

Questions about long-term use remain, despite new ideas regarding barriers to adherence. The increased availability and lower costs of drugs, and the advent of fixed-dose combinations, have raised hopes of reducing access problems by lowering cost.

Initiation and continued use are influenced by different factors, however, so attention has to be focused on use over the long term. Recent studies show that patients in Haiti and a number of African countries take about 90% or more of their drugs (19, 20). This gives cause for optimism. At the same time, however, lifelong use of drugs raises the question of sustainability, for which operational research may provide some insights (21).

A number of interventions (most of them tested in developed countries) have been conducted with antiretrovirals. Individualized education and advice have proved to be successful, especially when associated with participation in support groups. Scaling up treatment will mean sharing responsibilities with health workers who lack formal medical training – allowing health workers to monitor and follow up patients – and this will have profound implications. The extent to which the lessons from successful programmes can be rapidly implemented in diverse settings indicates a rich agenda for operational research, and the key role of innovative knowledge-sharing mechanisms.

Coping with toxicities

The importance of treatment-associated adverse effects in current HIV therapy is illustrated by several studies demonstrating that 40% or more of patients initiating highly active antiretroviral therapies will experience one or more forms of drug toxicity, and consequently may need to modify their regimen within the first year of treatment (22). Examples include hepatic toxicity, rash, diarrhoea, anaemia and peripheral neuropathy. Other adverse effects may become noticeable clinically only after more prolonged exposure to therapy (one to two years) (23, 24).

Innovative ways of assessing the potential toxicity of new drugs are needed at all preclinical and clinical phases of drug development. To ensure that millions of people get the best, sustained treatment, it is imperative that issues of resistance and longer-term safety and tolerability of treatment receive sufficient attention as treatment expansion unfolds. However, drug toxicities will always be preferable to inevitable death in the absence of drug treatment, particularly if concerns over toxicities prevent availability of treatment in resource-poor settings.

Preventing drug resistance

The issue of resistance by HIV to antiretroviral drugs is a major concern. Evidence from clinics, apart from clinical treatment trials, suggests that the frequency of incomplete virological suppression in people treated with combination therapies may exceed 50% (25). Incomplete suppression results in acquired viral resistance to antiretrovirals. Resistance often occurs to more than one or two of the three drugs that are being taken by the patient, because of cross-reactivity between drugs within a given antiretroviral family. While the emergence of a drug-resistant virus may be associated with a slower immunological decline in some people, virological failure of treatment places people at risk of developing resistance to antiretroviral drugs. They are also at risk of losing treatment options after treatment has been modified several times, and of ultimate immunological failure and morbidity.

Methods are needed that ensure the effectiveness of antiretroviral therapies in preventing virological treatment failure, and novel, more potent drugs will have to be designed that are active on both “wild” and resistant strains of viruses. Since current therapy is capable of suppressing viral replication but not capable of viral eradication

from the host, no current therapeutic regimen will be completely successful. Thus, reservoirs of infection are established early and apparently persist in all HIV-infected people irrespective of therapy (26). A systematic and rigorous approach to treatment offers the best opportunity to study and promote adherence and thereby reduce drug resistance and treatment failure (see Chapter 2).

Developing new drugs and strategies

Dozens of new drugs are being researched, including those belonging to the three currently available families of antiretrovirals: nucleosidic and non-nucleosidic reverse transcriptase inhibitors and protease inhibitors. Research and development of new compounds in these three families aims at providing drugs that are more potent, easier to take and better tolerated, as well as new formulations combining several of the drugs in one pill.

The first of a new class of "entry inhibitor" drugs that prevent the virus getting into cells in the first place was launched in 2003. These drugs will probably be the most important new antiretrovirals. They target human cell components, rather than viral components, and therefore the virus should find it more difficult to develop resistance to them. The next class of drugs expected is that of inhibitors of the integration of viral DNA into the host's genome.

The issues of toxicities and insufficient virological and immunological potency are not being solved by current treatment strategies. Therefore, new strategies need to be targeted at immune-based approaches to the treatment of HIV-1 infection, such as therapeutic vaccination, passive immunization or eradication of the "reservoirs" of infection. These approaches represent a vital area of basic and clinical research for the coming years.

Tackling tuberculosis and HIV/AIDS together

Tuberculosis (TB) impacts heavily on HIV morbidity and mortality, as HIV is the most potent risk factor for reactivation of latent tuberculosis infection to active disease. A person dually infected with HIV and *Mycobacterium tuberculosis* has an annual risk of developing TB ranging from 5% to 15%, compared with the lifetime risk of 10% for someone with an intact immune system.

One component of the strategy to decrease TB-related morbidity in people living with HIV/AIDS is to prevent the progression of latent TB infection to active disease, by offering isoniazide preventive therapy as part of the clinical package of HIV care. This treatment has been shown to reduce the risk of TB in tuberculin test positive HIV-infected individuals by 67% (27). Because of reinfection, however, the effect is relatively brief in communities where TB is endemic. The BCG vaccine for TB does not protect against primary infection and, on average, has a protective effect against active disease of only 50%. A crucial means of improving HIV-related morbidity will be the development of an improved TB vaccine. The many steps needed to identify TB infection, and the need to take treatment for at least six months with periodic evaluations for adverse reactions, mean that the proportion of individuals who complete treatment, even under the best conditions, is small.

In order for isoniazide preventive therapy to be an effective public health measure, further research is needed to understand how to diminish the loss of treatment candidates at each step of the process, and how to find effective, shorter-term treatment with few side-effects. New medication delivery methods (for example, medication skin

patches and other depo-preparations) are also required, as are new methods other than tuberculin skin tests to determine cases of infection.

OPERATIONAL RESEARCH

Pilot treatment programmes have been successfully conducted in several countries including Côte d'Ivoire, Senegal, Thailand and Uganda, clearly demonstrating that treatment in those settings is feasible, and that adherence to treatment, tolerance of therapy and incidence of resistance are no different from those found in developed countries (20, 28, 29). Expanding care and antiretroviral therapy to all those who need them worldwide raises a number of challenges for sociobehavioural, clinical and operational research. The term "operational research" refers here to an array of subjects and disciplines supporting the design and improvement of the systems that allow effective prevention, treatment, care and, ultimately, vaccines to reach all those who need them. It denotes the sciences underlying the rational organization of care, and might also be called "delivery system research". In its own way, its enquiries tackle problems as difficult and as intellectually challenging as those in the other three areas of research summarized above; the methods are not those of biomedical science, but rather of social science, economics, statistics, engineering, psychology and anthropology, among others.

Operational research, so defined, can help to involve, guide and coordinate the roles of care providers from government, the private sector, nongovernmental organizations, communities, faith-based organizations and the workplace, and to deliver antiretroviral therapy. Equally importantly, such research is needed to measure and monitor in a standardized way the impact of antiretroviral therapy in terms of parameters such as additional years of healthy life, fewer deaths, economic progress across society,

Box 5.1 Learning by doing – the operational research agenda

In treatment programmes it is critical to obtain data about what works, what does not work and why, and to have this information available as quickly as possible. This is implicit in the 3 by 5 strategy, where one of the two strategic elements in Pillar Five, "The rapid identification and reapplication of new knowledge and successes" (see Chapter 2), is to learn continuously by doing – with ongoing evaluation and analysis of programme performance and a focused operational research agenda.

The treatment initiative's operational research agenda has six areas of activity.

- *Coordinating and helping to develop an appropriate operational research agenda.* Consensus will be developed with programme managers about the immediate needs of antiretroviral therapy programmes, and the agenda will be reviewed regularly as data and evidence are generated and new issues emerge.
- *Seeking data on the impact of scaling up*

antiretroviral therapy. While treatment is expected to accelerate prevention, clear evidence is required that this does happen. Any negative interactions, such as stigma and discrimination, must also be identified rapidly so that they can be halted.

- *Identifying ways to define the effects of scaling up therapy on health systems performance.* The resource inputs and capacity building called for in line with the targets are expected to strengthen health systems. It is important to provide clear evidence that this does indeed happen, and to seek ways to facilitate it. It is equally important to see where the opposite is happening and to identify ways to minimize any negative impacts.
- *Identifying ways to cost and analyse antiretroviral therapy programmes.* The debate about whether treatment or prevention is more cost effective has been made redundant by the universal

recognition of the merits of a comprehensive approach. Nevertheless, solid cost data and cost-effectiveness analysis must be made available to help develop sustainable systems and their long-term financing.

- *Improving programme design and finding better tools.* The results of all operational research and other strategic information-gathering on risky behaviour and the evolution of drug resistance need to be analysed rapidly. The capacity of research groups in developing countries will be supported to enable most data analysis to be done nationally.
- *Incorporating new knowledge into policy and practice.* Data and new knowledge need to be fed back rapidly both to the centres where the research was carried out (an ethical obligation) and, more widely, to any programmes facing a similar situation. This core activity of WHO underpins the entire operational research approach.

development of drug resistance, and adherence to treatment (see Box 5.1).

Key issues to be tackled through operational research include:

- optimizing therapeutic regimens for scaling up therapy, for example by performing clinical trials and following up cohorts of treated patients;
- monitoring tolerance of therapy in trials and open patient cohorts;
- establishing optimal ways of monitoring therapy in the context of resource-limited settings; specifically, improving means of enumerating CD4 cell counts, measuring plasma HIV viral load and assessing viral resistance;
- building surveillance programmes to monitor resistance to antiretroviral drugs: when resistance develops to today's drugs, new treatments will be needed;
- improving diagnosis and treatment of opportunistic infections;
- seeking data on the impact of scaling up antiretroviral therapy on prevention and risky behaviour, mitigation, and stigma and discrimination, and using the data to improve programmes designed to reduce risky behaviours;
- identifying the consequences of antiretroviral treatment scale-up on health systems performance;
- creating peer-to-peer learning systems at the clinic, district and country levels so that new findings discovered in the field, combined with existing knowledge, can be quickly disseminated and applied;
- developing innovative, scalable models of how human resources in resource-poor settings can best be mobilized and trained to tackle HIV/AIDS prevention, care and treatment.

Economic issues

Economic research is essential to ensure that therapeutic strategies using antiretrovirals are successful in developing countries. Earlier cost-effectiveness analyses erroneously concluded that such treatment is not cost effective compared with other interventions, especially prevention. These studies did not adequately consider major issues such as the strong link between treatment and prevention (which are not substitutes but are complementary activities); the economic law of diminishing returns that makes prevention very effective at low levels of coverage but each additional input less effective as coverage approaches 100%; and the underestimation of the impact of HIV/AIDS on economic activity and development. Furthermore, they are now rendered obsolete by the huge fall in the cost of antiretrovirals that has since taken place.

Researchers have already linked the dynamic relationship between potential famine and the spread of HIV among rural agricultural workers; the relationship between HIV and malnutrition in general; and the effect of food insecurity on the autonomy of individuals, particularly women. Understanding the complex intersectoral relationships gives a better picture of HIV's true impact, and illuminates possible points of intervention (30, 31).

To discover and improve methods of scaling up access to treatment, economic analysis must be coupled with clinical data provided by longitudinal follow-up of patients in resource-poor settings. The cost-effectiveness ratio of different clinical and economic strategies will provide information that will help answer questions, such as: at what level can treatment ideally be initiated? What are the most effective strategies for switching regimens? How can biological monitoring be optimized? Economic research will also contribute to the identification and evaluation of different strategies of funding access to treatment. At the macroeconomic level, it will be important to establish

how the cost burden is distributed between domestic and international sources and, among domestic contributions, the share and incidence of out-of-pocket payments. At the microeconomic level, the effect of different financing arrangements on treatment adherence, the development of drug resistance, and final treatment outcomes will be significant topics of study.

Health policy analysis

It will be important to identify the factors that affect efforts to increase access to treatment, particularly in the context of health services. Some of the key factors are: leadership and management skills; sufficient and sustained funds for antiretroviral medications; technical competence in drugs and commodities procurement; training; monitoring of outcomes; and, in the public sector, a functioning district health system capable of delivering services. Research should include: identifying which factors increase or hinder integration of HIV/AIDS control programmes with public health policy and collaboration with other programmes; developing policies that support such collaboration and integration; and analysing the roles and comparative advantages of all the stakeholders involved in implementation of HIV/AIDS and other interventions.

Unsafe blood practices transmit infection



Wang Kai Jai's mother contracted HIV/AIDS after selling her blood to a hospital. In turn, Wang Kai Jai, now four years old, from Licheng, Hebei Province, China, became infected.

Many people living with HIV/AIDS have acquired the virus through

infected blood or blood products or by using unsafe blood donation facilities. In some areas of China, people eager to escape poverty sold their blood through middlemen who often reused needles.

Scaling up access to treatment must be used as an opportunity to promote global health reforms at the country level with benefits that go beyond HIV care. There is the potential to create effective incentives to improve health infrastructure in resource-limited settings. Research is needed to identify all the potentially negative and positive externalities of scaling up access and their effects on health systems.

Equity issues

Social inequality in the settings where care is to be implemented, the constraints on resources available for treatment, and the need to define eligibility criteria for the provision of antiretroviral drugs, all call for special attention to the equity dimension of the intervention. Special measures need to be taken in order to avoid the possibility of unwittingly reinforcing existing inequalities, setting up a two-tier system in allocating resources, or weakening other disease control efforts by giving priority to HIV/AIDS. In addition, care must be taken to protect the rights of patients when measures such as partner notification and disclosure are deemed to be necessary, and attention must be directed to the local conditions that may hamper confidentiality, especially when treatment is implemented on a large scale.

Many of the barriers that prevent disadvantaged members of society from accessing health care and obtaining treatment are a result of the deficiencies of health services, and there is a growing awareness that the treatment scale-up initiative represents an opportunity to tackle some of these shortcomings. Hence, it will be necessary regularly to review socioeconomic information about treated patients in order to make sure that poorer people have equal access to medication. More work is needed on the appropriate indicators of equity and how information can be collected about them.

Special consideration should be given to gender as it affects the provision of care. A better understanding is required of the particular circumstances that lead to discrimination against HIV-positive women, and of those conditions that enable women to respond and take control of their own affairs. It would be useful to keep track of programmes that have sought to integrate gender considerations into health services, which have an important role to play.

Another obstacle to care comes from the stigma that is attached to seropositive status, and concerted efforts to assess this information can help define locally effective strategies. There is little doubt that stigma and avoidance of testing and treatment are mutually reinforcing, and that it is precisely the individuals who are marginalized because of their status who are not reached by prevention and care efforts. The evidence base for what works in order to reduce stigma and why is, however, thin and has to be strengthened by well-designed studies, both to substantiate the effect of multiple interventions and to define the packages that are effective in different contexts (32, 33).

INTERNATIONAL COLLABORATION

Progress has been accelerating in international collaboration and coordination in HIV/AIDS research, which is critical to achieving the Millennium Development Goal of halting and reversing the pandemic by 2015.

Joint innovative actions, through global research networks and partnerships between the public sector, academic institutions, communities, the private commercial sector and civil society organizations, bring benefits greater than the sum of current high-quality but separate research projects. The benefits include quicker generation of

research findings, consensus on international standards for the conduct of research, and research capacity strengthening.

Collaboration permits parallel, concurrent efforts to obtain more timely answers to critical questions. Partnership across sectors through creative public-private alliances can contribute to faster progress in research by linking together diverse approaches and different stages of the research process (see Box 5.2).

International collaboration can lead to consensus on standards for the conduct of research which respect the human rights of study participants, support the research priorities of host countries, and promote community involvement in the design and conduct of research. Collaboration can also ensure that prevention and care interventions that are demonstrated to be safe and effective are rapidly made available to all study participants and to other members of the high-risk populations from which they were drawn.

International collaboration to strengthen research capacity enables the creation of a critical mass of researchers who can focus on national priorities, participate in policy-making bodies, and contribute to international research efforts. International and regional training partnerships must be complemented by active efforts to stem the brain drain from developing to developed countries, as Brazil, China and India are doing. This is achieved through investment in research and development to construct strategic knowledge-based industries that can employ nationals educated at home and abroad and attract expatriates to return.

Building national and international research infrastructures, laboratory capacity and improved surveillance systems; collecting, processing and disseminating data; and training basic and clinical researchers, social scientists, health care providers and technicians are all essential to efforts to accelerate knowledge creation. Such acceleration is required to respond to the scale of the HIV/AIDS pandemic. The substantial remaining challenge, and one to which the 3 by 5 initiative is directed, is to ensure that this knowledge immediately improves the lives of people most in need (34).

Box 5.2 Building partnerships in the fight against disease

The long-term struggles against poliomyelitis and tuberculosis (TB) have shown how international and multisectoral partnerships can work effectively to combat major diseases.

When the World Health Assembly established the goal of polio eradication in 1988, the need for a new kind of partnership was evident. The pioneering work to eliminate polio from the WHO Region of the Americas was initially carried out by a small group of partners, consisting of WHO, Rotary International, the United Nations Children's Fund (UNICEF) and the US Centers for Disease Control and Prevention. This group then grew to include the government of every country in the world, 30 major donor partners (contributing more than US\$ 1 million) and dozens of implementing partners, including national and international

humanitarian organizations and nongovernmental organizations.

To ensure effectiveness, a number of basic principles have guided work over the 15 years during which this group has worked together in pursuit of its common goal of a polio-free world:

- multisectoral representation;
- long-term commitment;
- top-level institutional representation;
- full use of comparative advantages;
- common operating principles and forums (for example, the work of the partnership was guided by a series of common, strategic plans covering several years, resource requirement documents and workplans at the international, regional and national levels).

As part of the campaign to combat TB, the Stop TB Partnership has become greatly respected globally. It includes WHO and the World Bank, and its strategic objectives have been formulated in close consultation with high-burden countries themselves. These objectives are directed towards the problems and policy priorities of the principal stakeholders, for example in relation to the United Nations Millennium Development Goals.

The Partnership has an increasing number of active participants. It has made significant progress against TB, highlighted work on new diagnostics, drugs and vaccines, and rapidly operationalized the Green Light Committee and Global Drug Facility to tackle lack of access to TB drugs.

Sharing knowledge

Extending treatment opportunities needs a faster research process than is available through traditional notions of research. The nature of the HIV/AIDS epidemic is changing quickly in many countries – too quickly to be effectively countered through standard research processes, whose timeline is typically measured in years. In addition, many of the decisions on which research projects are to be funded and pursued are made by policy-makers at some distance from the problem. As a result, resources and efforts are invested in work that may have little or no relevance to actual implementation in the field.

The public health community must rethink its definition of knowledge and the structure by which it is generated, shared and applied. The aims of knowledge management are to collect all relevant information and intellectual capital into a common system, and provide equal access to that information, ensuring that it can be synthesized with local needs. Such a system enables members of the public health community to

communicate directly with their peers on matters of mutual interest, such as effective practice in their own localities.

The 3 by 5 goal prompts public health practitioners to share and exploit experiential knowledge in a much more direct way, for example through “communities of practice” – informal networks linking individuals and groups who share common professional interests and who benefit from frequent exchanges of knowledge through the Internet or other telecommunication methods. Progress in information and communication technologies and other learning systems such as communities of practice gives cause for optimism. Improved communication can spur a knowledge revolution that will particularly benefit poor countries and communities, through greater use of the Internet, e-mail and telephone, and better satellite and wireless technology. By whatever means, the promotion and improvement of learning systems at all levels should greatly assist the achievement of public health goals as well as helping to strengthen health systems in general.

A mother's story



Gideon Mendel/Network

Nesta Mkhwanazi comforts her daughter, Samkelisiwe, who has been receiving antiretroviral treatment in the tuberculosis ward of Ngwelezane Hospital, KwaZulu-Natal, South Africa (see Samkelisiwe's story in Chapter 1).

“My daughter's recurring tuberculosis cannot be cured,” says Nesta. “She has also been tested and diagnosed with HIV/AIDS. This has

made life very difficult for us, as I have only a monthly pension of 500 rand [approximately US\$ 75] with which to support and care for my two daughters and four grandchildren. At 51 I find it hard to be a mother again to all these children. However, I am proud that my daughter has decided to disclose her HIV/AIDS status to our community and to help educate others about this disease.”

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