Challenges and opportunities for expanding HIV care and treatment: what can be

***Lisa R Hirschhorn*[1,2] *& Marie-Louise Newell*[3,4†]**

†Author for correspondence
[1]Harvard Medical School, Division of AIDS, Boston, MA, USA
[2]JSI Research and Training Inst., Boston, MA, USA
[3]University of KwaZulu Natal, Africa Centre for Health and Population Studies, Somkhele, South Africa
Fax:+27 355 507 565
E-mail: mnewell@africacentre.ac.za
[4]University College London, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London, UK

> "Traditional thinking is all about 'what is' – future thinking will also need to be about 'what can be'"
>
> Edward de Bono

Now well into the third decade of the HIV epidemic, we are entering a new phase in the clinical and public-health responses to the problem. Basic and clinical research has led to identification of the virus, a better understanding of the host response, development of effective treatments, and advances in prevention and care programs. At this time, attention is shifting to questions on how to ensure research and knowledge are appropriately translated into policy and practice and how to optimize programs in individual settings. In resource-limited countries, where the epidemic has taken its greatest toll, the answers to these questions will mean the difference between life and death for millions. This edition of *Therapy* aims to draw attention to efforts that have led to this new phase, while highlighting potential areas where research and programmatic attention should now be focused.

The area of prevention of mother-to-child transmission (PMTCT) is one example where much progress has been made, but more work is still needed. The article by McIntyre and Martinson reviews some of these successes, but also raises concerns, identifying areas in which further research and implementation are needed [1]. One area is the better understanding of optimal treatment for both mother and child after exposure to single-dose nevirapine for PMTCT and subsequent development of resistance to nevirapine, one of the main components of first-line treatment [2]. Other areas in which further research and efforts are needed include the optimal programmatic approach to ensure PMTCT for all pregnant women and systems to ensure that highly-active antiretroviral therapy (HAART) is used in resource-limited settings for pregnant women who meet clinical criteria for treatment of their own infection. Further areas for future work include developing a better understanding of safety for the uninfected children born to HIV-infected mothers and exposed to HAART, including prematurity and longer-term hematological and immunological consequences, as well as the need for an effective antiretroviral drug that can be reserved solely for PMTCT to preserve treatment options for women and their babies [3–5].

In addition to PMTCT, other areas of prevention are also on the cutting edge of translating research into practice. Male circumcision has recently been shown to be associated with a reduced risk of acquisition of infection for males, although the impact on risk for their sexual partners is still under study [6–8]. However, Rennie reviews the significant challenges that must be overcome to successfully implement circumcision as a public-health HIV prevention strategy [9]. He argues that the overall approach will require the integration of public health and rigorous evaluation in the translation from the clinical trial to practice, a hurdle that faces many of the new advances being brought to the field of HIV prevention, care and treatment. Even after implementation, the overall impact must be monitored to ensure that changes in behavior, such as increased partners or intercourse too soon after circumcision, do not decrease the protection found under research settings.

A different challenge to moving forward in prevention efforts is reviewed by Nuttal *et al.*, who use the example of vaginal microbicide agents to prevent HIV to highlight the challenges of developing a drug that will be predominantly marketed and used in resource-limited settings [10]. Companies find little to encourage them to spend resources on agents where not only are the potential financial rewards limited, given the predominant market in resource-limited settings, but where the licensing and other bureaucracy also put obstacles in the way. The challenges and potential lessons will be important not just for microbicides, but for other drugs needed to treat infections and conditions predominantly seen where financial resources are scarce.

Additional articles highlight some of the existing and future challenges of meeting the WHO goals of treatment for all in need [5,11–15]. To reach this goal, efforts will require the implementation

future medicine part of fsg

of effective approaches and the development of new treatments and prevention interventions. Rigorous research that is based in populations most in need will remain an essential component of these efforts, including clinical trials that are conducted in Africa and other resource-limited settings. Hakim and colleagues review the work done in these settings to date, highlighting the challenges of conducting rigorous clinical trials in the context of overwhelming need and ongoing limited care resources [16]. In the face of these potential barriers, they set out a bold and important agenda of questions that need to be answered. Although randomized clinical trials are often regarded as the gold standard in assessing the efficacy and safety of clinical interventions, results from such trials can be difficult to generalize to a nonresearch setting. We should not forget to integrate systems to evaluate the use and effectiveness of treatment strategies based on the results from clinical research into care in the real world [17].

The authors in this special focus concentrate on a number of areas where gaps exist in the effective translation from research into practice, or where the optimal approach has yet to be identified. These articles highlight challenges that are a growing priority as programs expand and mature. These include access, adherence, pediatrics and quality, and highlight the need for expanding the approaches to implementation of care and treatment and increasing research and evaluation to ensure that knowledge of how to treat and prevent is translated into effective and quality care.

Nachega and Mills review the findings from various settings that show that adherence to antiretroviral therapy (ART) in developing countries can be as good, or better, than is seen in the developed world, despite more challenging circumstances [11]. However, there is no time for complacency as there remains much that is unknown and it will require new efforts in research and implementation to ensure that these successes are maintained. This is of particular urgency to help patients maintain adherence to prevent failure as they face lifelong duration of therapy, an issue of particular importance in light of the limited treatment options currently available in resource-limited settings. Research is needed to develop support to improve or sustain adherence on an individual as well as population level, which may attract people who are not traditionally working in that capacity or that environment to come and work in the healthcare setting. Nachega and Mills also note that the existing challenge relating to the lack of healthcare professionals in many resource-limited settings will also have a potentially negative impact on the capacity to support adherence, highlighting the need for increased attention to creative approaches to expand the human-resource capacity and workforce.

These challenges in human resources, as well as in other elements of care and treatment, pose additional challenges to maintaining the quality of care required for maximum effectiveness and efficiency and are also addressed. With the first hurdle of getting people into ART programs being scaled up, issues relating to the quality of care are integral to the success of the programs. Hirschhorn reviews the current state of knowledge and practice in measuring and improving quality in the light of the rapidly expanding ART and HIV care program in developing countries [13]. She calls for increased work to more rigorously evaluate factors and models associated with the ability to provide and improve quality and outcomes of care.

One urgent area of high priority is the need to integrate HIV and TB treatment in order to tackle these two epidemics and optimize success rates in both TB and HIV treatment programs. This need has been underscored by the growing reports of people who are resistant to multiple or even all drugs used in TB treatment (multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis) in areas where the two epidemics overlap [18]. Wood reviews the barriers that have led to the challenges in managing these two epidemics, including the effect of coinfection on making treatment of either disease more challenging [14]. He identifies successful models and areas where treatment efforts need strengthening and ongoing work. The challenge of responding to their call for earlier access and treatment is reflected in the review of system needs for access written by Bärnighausen [12]. He highlights the importance of reliable estimates of need and people eligible (by whatever criteria) to be treated; and this call joins that of others for well-designed programs to monitor the epidemic and understand its dynamics.

Abrams highlights the achievements in resource-richer countries around prevention and care of pediatric HIV infection, and uses this information to contrast the statistics around transmission and pediatric deaths due to HIV in the regions where resources are scarce but HIV is prevalent [15]. The challenges at this stage are

primarily in translating scientific knowledge into an approach that will be feasible and able to reach a higher number of pregnant women for PMTCT and children in need of HIV care and treatment. Regardless of setting, Abrams also points out that challenges remain in understanding optimal approaches to delivery of pediatric HIV care, including the need for individualized dosing of medications and the complex development marking transition from infancy and childhood into adolescence, as children with HIV survive longer as a result of ART.

In the context of the enormous resources and efforts aimed at expanding ART coverage, there remains a growing challenge in determining the optimal regimens in these resource-limited settings, including presence of two other conditions including TB and pregnancy. Cooke reviews the potential for newer therapeutic approaches given the evidence of treatment-limiting toxicities related to stavudine, currently a component of first-line therapy in many countries, and the opportunities presented by decreasing costs and increasing availability of other less toxic but equally effective potential drugs [5]. New drug classes, while still expensive, will play a critical role in special groups, including pregnant women and patients on TB treatment, as well as providing better options for individuals for whom first-line treatment has failed. Defining optimal ways of managing these patients, choosing regimens, working to decrease costs and evaluating new approaches and regimens for therapeutic success and tolerability are all challenges that need to be met.

The authors who have contributed to this supplement bring a wide range of disciplines and many years of experience in research, practice and public health to bear. The challenges that they present and potential areas for further work that they offer will serve as a valuable roadmap for the next steps in policy, public health, research and practice.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utlilized in the production of this manuscript.

Bibliography

1. McIntyre J, Martinson N: Prophylactic regimens to prevent mother-to-child transmission of HIV and their effect on future treatment. *Therapy* 4(6), 797–805 (2007).
2. Arrive E, Newell ML, Ekouevi DK *et al.*: Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *Int. J. Epidemiol.* 36(5), 1009–1021 (2007).
3. Little K, Thorne C, Bunders M, Luo C, Ngongo N, Newell ML: Disease progression in children with vertically-acquired HIV infection in sub-Saharan Africa: reviewing the need for HIV treatment. *Curr. HIV Res.* 5, 139–153 (2007).
4. Thorne C, Newell M: Safety of agents used to prevent mother-to-child transmission of HIV – is there cause for concern? *Drug Saf.* 30, 203–213 (2007).
5. Cooke GS: Evolution of adult antiretroviral therapy for programmatic delivery in Africa and the potential role for new therapeutic approaches. *Therapy* 4(6), 767–774 (2007).
6. Turner AN, Morrison CS, Padian NS *et al.*: Men's circumcision status and women's risk of HIV acquisition in Zimbabwe and Uganda. *AIDS* 20, 1779–1789 (2007).
7. Gray RH, Kigozi G, Serwadda D *et al.*: Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 369, 657–666 (2007).
8. Bailey RC, Moses S, Parker CB *et al.*: Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 369, 643–656 (2007).
9. Rennie S: The ethics of using male circumcision for HIV prevention: exploring the middle ground. *Therapy* 4(6), 731–735 (2007).
10. Nuttal J, Douville K, Galbreath C, Walker S, Norick P, Rosenberg Z: Challenges of producing a drug primarily for use in developing countries: microbicides for HIV prevention. *Therapy* 4(6), 725–730 (2007).
11. Nachega JB, Mills EJ: Antiretroviral therapy adherence in resource-limited and resource-rich settings: current status of knowledge and research priorities. *Therapy* 4(6), 775–786 (2007).
12. Bärnighausen T: Access to antiretroviral treatment in the developing world: a framework, review and health systems research agenda. *Therapy* 4(6), 753–766 (2007).
13. Hirschhorn LR: Ensuring quality of care in the scale-up of HIV care and treatment in resource-limited settings: a challenge for all. *Therapy* 4(6), 737–744 (2007).
14. Wood R: Integrating the care of HIV and TB in developing countries. *Therapy* 4(6), 787–796 (2007).
15. Abrams EJ: Taking stock: triumphs and challenges in the field of pediatric HIV infection. *Therapy* 4(6), 705–709 (2007).
16. Hakim JG, Nhando N, Chisada A: Clinical trials in the use of antiretroviral therapy in developing countries: results and challenges. *Therapy* 4(6), 745–752 (2007).
17. Little K, Newell ML, Luo C, Ngongo N, Cortina Borja M, McDermott P: Estimating the number of vertically HIV-infected children eligible for antiretroviral treatment in resource-limited settings. *Int. J. Epidemiol.* 36, 1905–1913 (2007).
18. Migliori GB, Cirillo D, Centis R, Girard E, Raviglione M: Multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*: epidemiology and control. *Expert Rev. Anti. Infect. Ther.* 5, 857–871 (2007).