# The marriage of science and optimized HIV care in resource-limited settings

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Large-scale HIV management in resource-limited settings has been remarkably successful in a relatively short time frame. Once combination antiretroviral therapy (cART) became more universally available, national treatment programs were able to provide much of the needed therapy which was originally prioritized towards patients with the most advanced and symptomatic disease. At the time, it was thought that comprehensive laboratory monitoring for safety and efficacy was either unavailable, too expensive or would detract from the focus of providing life-saving treatment to as many individuals who needed it as possible [1].

The current worldwide expansion of antiretroviral therapy is due to a large broad-based international effort in financing the antiretroviral drugs and infrastructure required for delivering treatment and care. It is estimated that over 3 million patients are receiving antiretroviral therapy, with the majority of patients on treatment worldwide now being from resource-limited settings [2]. The fears that HIV/AIDS treatment would detract from other healthcare concerns or lead to widespread drug resistance have been unfounded. This shift in patient demographics has lead to the identification of new strategic, programmatic and political challenges. Important treatment-related issues that need to be addressed immediately have been identified by the relevant scientific communities. The fundamental scientific concerns fall into two categories: the comprehensive approach to care and treatment management in settings in which resources are limited, and the diversity of a variety of populations who are predominantly women, have heterogeneous viral subtypes and have exposure to different environmental co-pathogens. There is an urgent need to link science and clinical practice wherever it is taking place. The extensive experience already accumulated in Western countries, though of great value, may not always be useful or even relevant in the current resource-limited setting context. Transporting the success of a Western approach to treatment and management of HIV/AIDS verbatim is unlikely to happen in these settings because of several fundamental differences not present in the West [3,4].

As a result of the recent failure of the leading HIV vaccine candidate coupled with the failure of the first large microbicide prophylaxis trials, preventive HIV strategies have been significantly setback [5–8]. At this point, it is clear that cART is a critical and essential factor for sustaining the success in controlling individual disease as well as the pandemic. Offering optimized cART in resource-limited settings is not only a moral obligation, but also a necessity, which happens to be feasible and cost effective if life is to be preserved.

Addressing the need for the provision of rational guidelines for adult HIV-infected patient management

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in resource-limited settings is the focus of the WHO recommendations first published in August 2001 and updated in 2006 [9,10]. Many questions have emerged following the publication of this revised version. The lack of evidence addressing several key questions such as how to improve adherence, when to switch therapies, optimal treatment of pregnant women and important drug–drug interactions with antituberculous or antimalarial agents have underlined the need for re-defining key research questions. Directly observed therapy (DOT) has been proposed to minimize treatment failure due to lack of adherence, the most common cause of treatment failure. Although DOT may improve adherence when treatment is initiated at late stages of disease, whether this can be sustained lifelong remains questionable. Viral load monitoring is an area worthy of serious research attention [11,12]. Determining second and subsequent choice therapies is also an area open to further study. Current practice is empiric in most resource-limited settings; however, national or regional drug resistance surveillance programmes have been introduced with the support of WHO [http://www.who.int/drugresistance/hivaids/network/en/]. Although it is clear that truly optimal management may be impossible for each area or region in every country, this disparity should not be an excuse to limit resources and capacity development when and where it is possible.

Recent data indicate that providing cART to women from the third trimester of pregnancy up until the end of the breastfeeding period is an approach with significant benefit and therefore should be encouraged [13–15]. Implementing this strategy, completely routine in the West, as well as other interventions is critical if we are to turn scientific evidence into a real benefit for targeted populations. Regarding research, not only must we avoid any notion of academic colonialism, but also we must actively promote the development of expertise with supporting infrastructure, which will nurture and sustain the next generation of scientists in their respective countries.

Despite several limitations, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy is the preferred initial choice for treatment in most worldwide settings regardless of resources. This choice is based on data from large randomized studies done in the West, which have shown that the most 'effective' regimens are NNRTI-based [16]. The question remains, what is the best treatment choice for a person with limited second line options who still needs decades of therapy? Studies with endpoints at 48 and 96 weeks performed in Western countries will not answer this question for most of the world. Drugs from new classes, such as the integrase inhibitor raltegravir, with high potency, good tolerance, favourable resistance profiles and low manufacturing costs, need to be rapidly evaluated in all the settings in which they have the potential of providing lifesaving treatment alternatives.

Monitoring viral load is necessary to assess virologic treatment failure [11,12]. It has been demonstrated that higher viral load on treatment is associated with a greater probability of developing resistance. In particular, as the primary treatment in most areas is NNRTI based, the viral load threshold to define treatment failure of 10 000 copies/ml seems high because this level may allow for the more rapid and extensive development of resistance mutations [16,17]. Any other approach such as relying on clinical or immunological data to guide the switch decision will result in the accumulation of resistance mutations that can lead to difficulties finding an effective subsequent treatment regimen [18]. Where viral load testing is available, it should be used, where it is not, it should be developed, and, overall, viral load testing should be considered in the total cost of appropriate patient care. The research question should be how often viral load testing is performed once a patient has optimal viral suppression. This can only be answered by clinical studies in the relevant settings.

Primary resistance surveillance and evaluation of its impact on disease progression and response to treatment is another goal to reach in resource-limited settings in the short term. Genotyping will become more necessary in the near future, and we must act now to develop national reference centres capable of performing this relatively sophisticated assay in each country or region.

An example that highlights relevant needs in regard to resistance testing in the developing world is the unexpected resistance patterns observed with thymidine analogue-based treatment. It has now been reported from multiple centres in resource-limited settings that the K65R mutation may appear during treatment failure without tenofovir exposure at rates up to 5%, a phenomenon rarely seen in the West [17–21]. Is this subtype related or due to time on failing thymidine-based regimens? This is an important question that may impact recommendations for first and second line therapy. Regarding the new drugs, the effect on a diverse genetic population early on in the development process is critical if these drugs are to be used effectively worldwide. We cannot afford to wait for 5 years after the approval of a drug to find out it has a suboptimal effect in certain populations.

In order to benefit populations in need, relevant clinical data are urgently needed, including drug efficacy in genetically diverse populations, most cost-effective and efficient monitoring of therapy and interactions with drugs to treat common co-infections and diseases. Data collection, monitoring, analysis and evaluation that are managed outside the countries must now be done in countries where the work is performed. Transfer of competencies must be done as this is essential for operational research. In addition, we must promote and strengthen national reference centres and develop high-level skills for the next generation of scientists and

clinicians. This is the only way in which we can assure a high and sustainable level of the needed expertise.

The clinical management issues are universal: training, testing, treatment choice, monitoring and where and when to use new drugs with new targets. The concept of what is 'optimal' for patient care can no longer be ethically looked at as a dichotomy, with those in the Western countries receiving the optimal care, and those in resource-limited settings receiving something much less than optimal.

Control of the HIV pandemic is now the primary objective. We need to learn more about optimal treatment choices and monitoring schemes appropriate in diverse resource-limited settings. We must build upon our existing and extensive knowledge base and target highly relevant research towards the affected populations in the countries where the patients reside. The international scientific community must address this urgent need with academic, social, scientific and economic support for the necessary critical research and training so desperately needed.

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