Clinical trials in the use of antiretroviral therapy in developing countries: results and challenges

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Clinical trials are regarded as the gold standard in the evaluation of the efficacy and safety of clinical interventions. The escalation in the use of antiretroviral drugs in developing countries has provoked many questions and concerns that require resolution and guidance through the rigors of clinical trials. While several centers of excellence have emerged in developing countries with the capacity to perform robust and ethically acceptable clinical trials, these are few and far between. Many interventions are therefore implemented on the basis of empirical evidence or based on findings in the developed world extrapolating from patients and circumstances far removed from realities in developing countries.

The therapy of HIV in developing countries has undergone a radical paradigm shift since the realization that antiretroviral therapy (ART) is not only feasible but can make a dramatic change in mortality and morbidity [1]. Many experts in the field hold the opinion that clinical trials provide the most reliable basis for evaluating the efficacy and safety of new treatments. Nonetheless, well-conducted observational studies are important in the determination of long-term safety of and choice of interventions [2]. Several factors that modulate the HIV epidemic and disease progression necessitate the conduct of clinical trials in developing countries to provide the basis for the use of ART in this environment. Factors that may require the performance of clinical trials for interventions that have been shown to be of proven benefit elsewhere are both scientific and socioeconomic. These include the clinical states of the majority of patients presenting for ART in developing countries. Anemia, poor nutritional states, comorbidities, lower CD4 counts, pediatric HIV disease and non-B HIV subtypes are important considerations in these environments [3–6]. The sheer number of a predominantly ART-naive patient population requiring evaluation and treatment often demands rethinking of treatment choices and strategies necessitating consideration of clinical trials in resource-constrained settings to facilitate the roll-out of ART. Studies are needed to address the issues of when to start ART, what drug combinations to start treatment with, what drugs to switch to and how to monitor ART, even though many studies in well-resourced settings continue to address most of these issues. In addition, there is an urgent need for capacity building to conduct clinical trials and to promote the highest ethical principles in research in the developing world.

Data sources

A PubMed search was conducted online for English-language publications using the terms 'clinical trials', 'ART', 'developing countries', 'capacity development' and 'ethics'. The clinical trials website [101] was searched for studies on ART in developing countries. We further reviewed reference lists and bibliographies for articles on ART in developing countries that made reference to clinical trials of ART initiation, antiretroviral drug switches, ART strategies and ethics in the conduct of clinical trials and capacity building for research.

When to start ART

The treatment of HIV has seen a marked shift from the early days of hit early/hit hard [7]. A swing to a less aggressive approach followed, recognizing that ART is associated with several concerns, including adverse events, resistance and adherence issues, and above all there are no prospects of eradicating the HIV virus at present. With better experience of the use of antiretroviral drugs, and the discovery of more drugs belonging to both older and newer classes, the debate of whether to start ART early during the course of HIV disease progression or wait until some measure of immunosuppression is demonstrated has again become topical. The two issues to balance are the need to suppress viral replication and achieve immune reconstitution on the one hand and to gain the best short- and long-term benefits from medication on the other. Germane to this argument is the fact that in

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developing countries most patients will inevitably be managed under a public-health program that has limitations of both human and material resources [8].

During the pioneering days of combination ART, the thought of using expensive branded drugs in developing countries was not an option for the majority of patients. The Durban International AIDS conference of 2000 acted as a catalyst, prompting many groups to provide ART in limited but well-documented ART programs [9–11]. Indeed, analysis of cohort studies has demonstrated that ART has similar efficacy in developing countries as in the developed world [1], although mortality is reported to be higher in developing countries [12]. In the ART in lower-income countries collaboration versus ART cohort collaboration comparison, at 6 months the median number of CD4 cells gained (106 vs 103 cells per µl) and percentage of patients reaching HIV-1 RNA levels lower than 500 copies/ml (76 vs 77%) was similar between high-income and low-income countries [12]. Data on when to start ART in developing countries based on clinical trial findings are lacking in adults. However, the CHER study conducted in South Africa addressed this issue in infants in a well-designed trial [13]. This study was modified by the data safety and monitoring board prematurely, as there was clear evidence that starting ART within the first 12 weeks of life reduced mortality by 75% (10/252 [4%] vs 20/125 [16%] deaths after a total of 246 person-years of follow-up; hazard ratio: 12.2; 95% CI: 8.2–17.4; $p = 0.0002$). Guidelines for the initiation of ART have been derived from experience of the use of ART in the developed world and on empirical considerations. The WHO has played a leading role in putting together guidelines that have been adapted and modified by many developing countries [8,14].

Choice of antiretroviral drugs for the initiation of ART

Combination ART is the mainstay of the treatment of HIV. The classes of antiretroviral drugs with which there is most experience are the nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs and NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Several new classes of antiretroviral drugs have been developed, including, integrase inhibitors, fusion inhibitors, CCR5 inhibitors, and so on. Experience of therapy of HIV in developing countries has largely been based on the three older classes of drugs. Most developing countries advocate initiating ART with a combination of one NNRTI plus two NRTIs, leaving PI-based regimens for treatment of failure or for use in special circumstances. The two combination options are promoted interchangeably in developed countries, in addition to the availability of pretreatment resistance testing and the capacity to switch to newer classes of ART for various clinical scenarios, such as the occurrence of comorbidities. An important concern that has emerged since the findings of the landmark HIVNET 012 study [15] is the widespread adoption of the use of single-dose nevirapine for the prevention of mother-to-child HIV transmission in developing countries. The demonstration of the emergence of resistance to nevirapine in women and children exposed to the drug in this way has caused concern regarding the efficacy of the later use of nevirapine in combination therapy in the mother and child [16,17]. Lockman *et al.* have shown that there is indeed a high failure rate if a nevirapine-based regimen is used within 6 months of the administration of the single-dose nevirapine (0% of women in the placebo group vs 41.7% in the nevirapine group [$p < 0.001$] experienced virologic failure) in a clinical trial in Botswana [18]. However, nevirapine-based ART used beyond 6 months after exposure to single-dose nevirapine results in similar rates of failure as those observed in non-exposed women: 7.8 versus 12% ($p = 0.39$) for placebo and nevirapine groups, respectively.

Antiretroviral drugs switch

Switching of antiretroviral drugs may become necessary for toxicity or because of the occurrence of treatment failure. With the advent of generic drugs produced for either in-country use, such as in Brazil and Thailand, or with a large export thrust, such as in India, some rigidity has emerged regarding which drug combinations are promoted in a given country. Stavudine-based regimens have been popularized because of their low cost, especially when coformulated with nevirapine and lamivudine in fixed-dose combinations (FDC). Recognition of the deleterious adverse effects of the stavudine component in the FDC, such as peripheral neuropathy, lactic acidosis and lipodystrophy, has raised concerns regarding the continued recommendation of this drug as a component of first-line treatment combinations. Indeed, the WHO has advised the use

of a ceiling dose of stavudine of 30 mg twice-daily for adults, even for those weighing more than 60 kg, based on findings in a number of studies [19–21]. It has also been recognized that zidovudine used in first-line combinations in developing world settings may result in the development of severe anemia, which, without adequate patient education and health facilities, could be fatal. In the Development of Antiretroviral Therapy in Africa (DART) study, the cumulative incidence of grade four anemia by 48 weeks of ART was 6.9%, a higher incidence than in studies from industrialized countries [22]. Such issues are a great worry when treatment is being task-shifted to lower levels of the health delivery system. We did not find clinical trials that addressed switching of antiretroviral drugs for treatment failure in developing countries.

ART treatment strategies

ART interruption studies with a variety of designs have been carried out in developing countries. The DART study looked at a cycle of 3 months off and on ART [23]. The incidence of morbidity was found to be higher in the treatment-interruption arm compared with the continuous-treatment arm (6.4 vs 2.4 events per 100 person-years; $p = 0.007$) [23]. Trivacan looked at two interruption strategies; a fixed-duration (2 months off and 4 months on ART) and a CD4-guided strategy (interruption and reintroduction thresholds of >350 and <250 cells/µl) [24]. The Staccato randomized trial in Thailand, Switzerland and Australia showed that there was a high failure rate in a 1-week off, 1-week on strategy [25]. However, in the same study comparison of a continuous treatment strategy versus a strategy of scheduled interruptions at CD4 counts above 350 cells/µl and resumption of treatment below 350 cells/µl showed no difference in viral suppression between the two arms (90.5 vs 91.8% in the interruption and continuous-treatment arms, respectively) [25]. The incidence of severe morbidity was higher in the CD4-guided strategy compared with the continuous-therapy group (17.6 vs 6.7 events per 100 person-years; $p = 0.001$) [24].

ART & concurrent therapy for opportunistic infections & AIDS-related malignancies

The use of ART in patients with opportunistic infections (such as TB and cryptococcal infection) and HIV-related malignancies (such as Kaposi's sarcoma) is an area that is particularly important in developing countries because of the frequent occurrence of these conditions in HIV-infected patients. The timing of initiation and the choice of ART is important in relation to the administration of anti-TB therapy because of drug interactions, immune restoration inflammatory syndrome, pill burden and so on [26]. Cryptococcal meningitis is a common AIDS-defining illness in severely immune-compromized patients who require urgent consideration of ART [27]. Whether to start ART concurrently with antifungal treatment or to treat cryptococcal disease first remains a contentious issue that has not been addressed through clinical trials. Kaposi's sarcoma is a very common malignancy in many developing countries, especially in sub-Saharan Africa [28,29]. This condition, which was one of the most important markers of AIDS in the developed world in the pre-HAART era, has now become less common, and indeed the use of ART appears to have resulted in marked reduction in its incidence. The impact of the roll-out of ART in developing countries on the incidence and prevalence of Kaposi's sarcoma has not yet been felt. There is an ongoing clinical trial in South Africa on the use of ART in Kaposi's sarcoma, but this study has not yet reported final results [30].

Laboratory monitoring of ART

The cost of ART has gradually come down to levels when it is no longer the prime limiting factor in the roll-out of ART. Indeed, through special pricing, providing ART at a cost of US$1 a day or even less is possible in many developing countries. However, an important hurdle to the implementation of the antiretroviral roll-out program is the availability of laboratory monitoring. Laboratory monitoring for drug toxicity and for efficacy/failure is often prohibitively expensive and can limit the implementation of ART programs. Simple laboratory tests such as hemoglobin and albumin have been used to guide initiation and monitoring of ART [31–33]. Nonetheless, the use of surrogate markers (CD4 count and viral load) remains the gold standard for the monitoring of ART. There is therefore a concerted effort to develop cheaper methods to perform CD4 count and viral-load assays, with the main aim of making these affordable and available in developing countries. Other surrogate markers such as p24-antigen assays have been on the wings for several years as potential markers for monitoring of viral suppression [34],

but we did not find clinical trials evaluating the use of this marker. One of the objectives of the DART clinical trial is to determine if ART can be given safely without intense routine laboratory monitoring [35]. This study is still underway and is yet to report findings on this objective. Several other clinical trials evaluating clinical monitoring versus laboratory monitoring in developing countries will be reporting in the next few months or years.

Clinical trials capacity development

The capacity to perform clinical trials that satisfy good clinical practice (GCP), good clinical laboratory practice (GCLP), human subjects protection training and other parameters is present in a limited number of centers in developing countries. A few examples of such centers of excellence include Fiocruz in Rio de Janeiro, Brazil, Impacta in Lima, Peru, Research Institute for Health Sciences in Chiang Mai, Thailand, YRG Care in Chennai, India, Joint Clinical Research Centre in Kampala, Uganda, and several university-based and state-funded research organizations in Asia, sub-Saharan Africa and South and Latin America. These centers, which have the infrastructure to carry out clinical trials of high standard, are few and far between. There is therefore a need to continue developing capacity to perform clinical trials to the highest standards. The ability of some centers in developing countries to perform clinical trials is often hampered by a lack of resources to conduct GCP, GCLP and human subjects protection training in a manner and frequency that satisfies the complex regulatory requirements of external funders. The availability of incountry trainers and the use of online resources would greatly facilitate training in these areas. Many leading organizations around the world, including the National Institutes of Health (USA), Medical Research Council (UK) [36], ANRS (France), NACCAP (Netherlands), the Bill and Melinda Gates Foundation, the Rockefeller Foundation, the Doris Duke Foundation, the Wellcome Trust, and organizations in Australia, Canada and other well-resourced countries, have developed collaborative research programs with centers in developing countries, with a major thrust to establish capacity and to conduct clinical trials of the highest standard. The recent announcement by the European Developing Countries Clinical Trials Partnership (EDCTP) to establish networks of excellence in Africa is a welcome initiative that will add to the efforts by the older organizations. The ultimate aim of performing clinical trials is to generate credible evidence to guide policy. It is therefore important that clinical trials centers focus on priority research questions relevant to their countries and regions [37]. The impetus to perform clinical trials is therefore the recognition of the need to have evidence for interventions in high-priority areas (see **Box 1**). HIV/AIDS research worldwide is largely supported by resources from wealthy nations. Developing countries must recognize the need to commit substantial resources from their budgets to conduct relevant health research. Strategies must also be formulated to translate research findings to policy, with community engagement as an important component of such strategies.

Ethics in clinical trials

When the WHO took stock of its '3 by 5' initiative, 1.3 million people were estimated to be on ART in developing countries by the end of 2005 [38]. This was short of the 3-million target but a big leap from the meager figure of 400,000 people on ART by the end of 2003. ART use is increasing rapidly, prompting many questions regarding its proper and effective use in the developing world. To answer these questions, properly designed and appropriate clinical trials are needed. In addition to the capacity to conduct clinical trials, the ethics of clinical trials in developing countries has come under the spotlight. Some of the issues that are of concern include 'uniform care requirement' and post-trial access to antiretroviral mediation [39,40]. Uniform care requirement is the belief that all clinical trial participants must receive a level of care equivalent to the world's best. Killen *et al.* challenge this notion and have argued that insistence on uniform care requirements may ignore other equally important ethical principles [39]. They emphasize that to be relevant, research must be responsive to the biological, epidemiological, sociological and political factors that affect the course of the epidemic in developing countries, and this includes severe global inequity in the distribution of health resources [39]. In the Helsinki Declaration, paragraph 30 states that at the conclusion of the study, every participant entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. There is no uniform agreement on this principle, and even within developing countries, regulatory authorities have changed their stance over time. Some authorities have factored into their consid-

Box 1. Priority research questions.

- At what CD4 count level does initiation of antiretroviral therapy ensure the best short- and long-term outcomes?
- What antiretroviral drug combinations achieve the best early and long-term therapeutic dividends?
- What second-line antiretroviral drug switches give patients the best long-term benefits?
- What antiretroviral drug choices and strategies best address therapeutic concerns peculiar to children?
- Which laboratory tests and how much laboratory monitoring are necessary to enable optimal individual and public healthcare?
- What is the best balance in research resource provision between governments and external funders to guarantee high caliber research on the one hand, and independence in priority research setting on the other?
- What are the benchmarks in ethical principles to guide clinical trials in culturally diverse settings?

erations the fact that sometimes proof of efficacy and safety in the local environment have brought about changes (e.g., cost of antiretroviral drugs) that have facilitated availability of such interventions for their communities. Properly constituted and well-trained ethics committees are important in ensuring that ethical concerns are addressed in clinical trials in developing countries. In addition, there is a need to carry out studies that evaluate the application of ethical principles in developing countries [41].

Discussion

ART has taken center stage in the response to the HIV epidemic in developing countries [1]. Nonetheless, the importance of prevention and other responses must not be underplayed [42]. There is a dilemma in the quest to achieve wide coverage through a public-health-oriented roll-out [8], and the need to provide evidence to back up major recommendations in the use of ART. Owing to the emergency nature of the epidemic, it is prudent to continue the current pragmatic approach, which draws from knowledge of the use of ART gained in developed countries and through empirical considerations, but without losing sight of the need to do relevant and appropriate research to guide pertinent and emerging questions. Clinical trials are the linchpin of evidence-based practice, and hence the need to ensure that most important decisions regarding the use of ART are subjected to this litmus test. Central to the conduct of priority-driven relevant clinical trials is the need to ensure that there are sufficient institutions in the developing world to conduct high-caliber research capable of withstanding the most rigorous scrutiny internationally. Several centers of excellence exist in developing countries, but the nature and the magnitude of the epidemic demands more centers with even better capacities and resources to cope with the constantly evolving therapeutic demands of this disease. Equally important is the need for adequate funding for research by both local governments and grant-awarding agencies. The Sydney declaration at the International AIDS Society meeting of 2007 emphasizes the need to allocate at least 10% of HIV money to research to ensure that there is better understanding of the disease and a more efficient deployment of interventions.

Future perspective

The use of ART in developing countries was insignificant before the advent of initiatives such as the Global Fund for AIDS, Tuberculosis and Malaria and the Presidential Emergency Plan for AIDS Relief. We must, however, recognize that some countries made inroads in this regard with proactive national initiatives such as the antiretroviral programs in Brazil and Thailand. Although the roll-out of ART has sometimes failed to achieve intended goals such as the '3 by 5' initiative, there is nonetheless hope that at last something tangible is being done for AIDS sufferers in the developing world. In the next decade, one expects this pace to continue or even accelerate as infrastructure and strategies such as task shifting are implemented. We envisage that issues such as the choice and availability of second-line drugs, and resistance testing to guide treatment options in second-line therapy, in particular, will increasingly become important issues to address. Long-term drug toxicities such as lipodystrophy, dyslipidemia and their consequences will gain prominence in developing countries. The choice of drugs for first-line therapy will therefore continue to be topical.

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Executive summary

Clinical trials in the use of antiretroviral therapy (ART) in developing countries

- Clinical trials are a key tool in guiding the use of ART. Well-conducted observational studies, however, can play an important role in determining long-term safety and choice of interventions.

When to start ART

- Clinical trials in adults are lacking, but in children the CHER study showed that starting ART within 12 weeks of birth reduced mortality by 75%.

Choice of antiretroviral drugs for the initiation of ART

- In women exposed to single-dose nevirapine for prevention of mother-to-child-transmission of HIV, the use of non-nucleoside reverse transcriptase inhibitors (NNRTI) regimens resulted in a high failure rate (41.7 vs 0%) when used within 6 months of nevirapine exposure. However, when used beyond 6 months there was no statistically significant difference in efficacy.

Antiretroviral drugs switch

- A ceiling dose of stavudine of 30 mg twice daily in adults has been recommended for all body weights in the hope of reducing the adverse events seen with this drug.
- During zidovudine use anemia needs to be carefully monitored, especially if ART is administered by lower cadres of staff.

ART treatment strategies

- Both fixed-dose and CD4-driven structured treatment interruption strategies have been shown in some studies to be inferior to continuous ART administration. These strategies are not recommended as an ART option at present.

ART & concurrent therapy for opportunistic infections and AIDS-related malignancies

- Concurrent use of ART and specific therapy for tuberculosis, cryptococcal meningitis and Kaposi's sarcoma (as examples of common co-morbidities) have been insufficiently studied. Clinical trials are needed to provide guidance on how to manage HIV and these conditions when they co-exist.

Laboratory monitoring of ART

- The cost and availability of laboratory facilities can be a hindrance to the roll out of ART even when drugs are affordable. Studies are underway to show if it is safe and effective to use limited laboratory monitoring to guide ART.

Clinical trials capacity development

- There is need to expand the limited capacity to perform clinical trials in developing countries to help answer the many questions that arise when using ART.

Ethics in clinical trials

- Whether participants in clinical trials in developing countries should receive care equivalent to the world's best, or what options are acceptable for post-trial care, are a few thorny ethical issues that must be addressed during the conduct of clinical trials in developing countries.

Conclusions

- There is need to conduct clinical trials in developing countries to guide use of ART because of the peculiar circumstances of patients in this environment, such as advanced disease at presentation (poor nutritional state, anemia, etc.) and issues related to the access of ART to large numbers of patients who require management under considerable limitations of infrastructure.
- There are only a few sentinel clinical trials that have helped shape ART policy in developing countries, and many more are needed to answer both perennial questions and emerging problems in the use of ART.

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