

Delivering pediatric HIV care in resource-limited settings: cost considerations in an expanded response

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If children are to be protected from HIV, the expansion of PMTCT programs must be complemented by increased provision of paediatric treatment. This is expensive, yet there are humanitarian, equity and children's rights arguments to justify the prioritization of treating HIV-infected children. In the context of limited budgets, inefficiencies cost lives, either through lower coverage or less effective services. With the goal of informing the design and expansion of efficient paediatric treatment programs able to utilize to greatest effect the available resources allocated to the treatment of HIV-infected children, this article reviews what is known about cost drivers in paediatric HIV interventions, and makes suggestions for improving efficiency in paediatric HIV programming. High-impact interventions known to deliver disproportional returns on investment are highlighted and targeted for immediate scale-up. Progress will carry a cost - increased funding, as well as additional data on intervention costs and outcomes, will be required if universal access of HIV-infected children to treatment is to be achieved and sustained.

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Introduction

The global push for the elimination of childhood HIV has led to increased coverage and improved design of prevention of mother-to-child transmission (PMTCT) programs [1]. Increased coverage and effectiveness of PMTCT has reduced the number of infant HIV infections and slowed the rate of increase in the burden

of childhood HIV. Despite these efforts, the burden remains high and continues to increase. There are approximately 3.4 million children infected with HIV with nearly 1000 more infected daily [2]. The majority of infected children are unable to access treatment; indeed, only three out of 10 children in need of antiretroviral (ARV) therapy (ART) globally receive it, an unmet need of more than 1 million children [3,4]. This carries grave

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consequences, as most HIV-infected children who do not receive treatment die early, up to 80% by age 5 years [5]. While elimination is the goal, the singular pursuit of this goal to the detriment of treatment will leave many children with little hope of survival. If children are to be protected from HIV, the expansion of PMTCT programs must be complemented by increased provision of pediatric treatment.

The provision of pediatric treatment for HIV and AIDS, particularly ART, is expensive. Overall, 77% of international AIDS assistance in 2011 was provided bilaterally, and 23% multilaterally. In 2011, the United States (US) was the largest donor to this effort, accounting for more than half (59.2%) of disbursements by donor governments [6]. Unlike adult HIV treatment, childhood HIV treatment will not lead to immediate economic gains associated with individuals being able to return to work or other productive activities. Thus, the argument cannot be made that compared with other child health interventions, pediatric HIV treatment is cost-effective. The challenge then is to articulate an argument that can justify expansion of PMTCT and pediatric treatment.

In highly resource-constrained settings, it is not possible to justify the prioritization of childhood HIV treatment on the grounds that it is a cost-effective child-health intervention. If the goal is to improve child health, there are other interventions that would achieve that end more efficiently (i.e., treatment of malaria, diarrhea, neglected tropical diseases). If the goal is to improve the health of children born HIV-infected, the situation is different, as there are no alternatives.

The humanitarian argument is obvious; it is the global community's responsibility to provide every opportunity for HIV-infected children to thrive. The equity argument stems from the large-scale investments in adult HIV treatment; if we deem that HIV-infected adults deserve treatment, then the same should apply for children. But in truth, children have not received the same amount of investment as adults. The fundamental right to life provides additional justification from the perspective of children's rights. The ultimate determination of the importance of prioritizing resources to childhood treatment of HIV is, therefore, determined by the relative weight an evaluator places on its efficiency as a child-health intervention versus humanitarian, equity and rights based arguments for the prioritization of HIV-infected children.

There are, however, humanitarian, equity, and children's rights arguments to justify the prioritization of HIV-infected children and the provision of appropriate pediatric treatment [7,8]. These arguments hold weight for many governments and donors for whom pediatric treatment is a stated priority.

This suggests that one or more of the humanitarian, equity, and child rights justifications have been given weight. That it is a priority despite there being more cost-effective child-health interventions does not imply that efficiency is not a critical consideration. The costs and relative efficiencies of different approaches to pediatric HIV treatment must be considered if the available resources allocated to the treatment of positive children are to be used to greatest effect. With a limited budget, inefficiencies cost lives, either through lower coverage or less effective services.

If program designers and managers are to give due consideration to the relative efficiency of different approaches to pediatric treatment, the costs and effectiveness of alternatives should be examined. In this article, we focus on the costs. Costing programs allows for the identification of critical cost drivers, and informs efforts to redesign programs to be more efficient. With the goal of informing the design of efficient pediatric treatment programs, and program expansions, this article reviews what is known about cost drivers in pediatric HIV treatment interventions. The article begins with an examination of what should be included in the costing of a pediatric program and moves on to highlight cost drivers before concluding with a discussion of how an understanding of these might inform program design.

Childhood HIV treatment and its cost

Costing of HIV treatment is complex; however, it is critical to support program planning and budgeting processes. The cost of providing care to an HIV-infected child depends on which services are being provided and who is providing those services. A better understanding of costs also helps to explore opportunities for promoting greater efficiencies and cost reductions. This is particularly critical in resource-constrained settings where the cost of scaling-up programs must be balanced against assurance of sustainability.

There are a variety of factors that must be considered in calculating costs and costing exercises may focus on costs at the facility, household, community, or program level. Full costs may be calculated to understand the value of all resources being utilized, including infrastructure and administration, but incremental costing may be more useful to estimate the impact of the introduction of new interventions. Actual expenditures on goods and services, or financial costs, can be calculated, though economic opportunity costs (i.e., those associated with lost productivity due to illness or death) more closely represent an actual society value. Additionally, significant variation exists across countries, and these vary depending on whether services are received from tertiary, secondary, or primary level health facilities. The availability of skilled

healthcare workers, laboratory equipment for tests, and other support services at tertiary facilities may make those more expensive.

Costing pediatric interventions has not received the same level of attention as the costing of adult programs [9–11]. As a result, data are often adapted from adult programming to estimate the cost of pediatric care. This is problematic as pediatric programs have unique characteristics that may not be considered if adult programs are used as the baseline. Several of these considerations influencing the costs of treatment for children are outlined and discussed below in the context of new 2013 WHO guidelines and global targets to eliminate childhood HIV/AIDS. Summary of cost drivers for consideration in pediatric care and treatment is as follows:

- (1) Outpatient care for infected children, including early infant diagnosis (EID) visit and follow-up.
- (2) Pediatric formulations for ART and supply chain strengthening.
- (3) Guidelines/protocols specific for pediatric therapy, including first-line and second-line therapies.
- (4) Laboratory monitoring including PCR for diagnosis.
- (5) Pediatric case finding and retention for children.
- (6) Human resources and training specific to children.
- (7) Physical and other infrastructure.
- (8) Other services specific to pediatric HIV care such as nutritional support, cost of supportive supervision, and so on.

Cost drivers of pediatric HIV treatment

A review of the literature leads to the identification of several important cost drivers. Below we focus on the most critical, those that have a large influence as drivers of program costs that can be influenced by program design. The costs associated with prevention of transmission from mother-to-child during pregnancy and breastfeeding are discussed in detail in other articles in this series (see Beyond PMTCT paper in this series). The cost drivers discussed include ARV drugs, laboratory procedures, approaches to case finding and retention, timing of treatment initiation, and human resource strategies. Program-level costs are important as well, with methods for efficiently optimizing program-level spending a priority area for additional work and research. In addition, PMTCT programming and the maintenance of such infrastructure contributes substantially to costs associated with pediatric HIV care and is impacted by population size, unit cost of reaching target populations, choice of ARVs, and scope of the intervention [12]. A detailed consideration of its impact in this regard is beyond the scope of this article, and PMTCT is discussed in detail in other articles in this series (see Beyond PMTCT paper in this series).

Antiretroviral drugs

Market dynamics

A significant driver of cost in HIV treatment programs for all ages are ARV drugs, which account for up to 50% or more of programmatic expenses [13–16]. Pediatric treatment is no exception. Moreover, a number of aspects of pediatric treatment lead to a unique set of drug cost issues related to the dynamics of the market.

Adult ART formulations are unsuitable for use in infants and younger children who have specific dosing and administration requirements. In the early years of HIV programming, the high cost of specially formulated pediatric medication was one of the main barriers to accessing pediatric HIV treatment. Before 2005, most pediatric ARVs were produced by innovator companies as single drugs, in both solid and liquid forms [17]. In an attempt to improve market dynamics and motivate companies to produce pediatric ARVs, stakeholders have promoted research to test and approve affordable and child-friendly products. Increasingly, recommended first-line drugs are available in child-friendly formulations of generic and fixed-dose combinations, which combined with user-friendly weight-based dosing, have vastly simplified pediatric treatment [17]. Child-friendly ARV formulations together with increasingly uniform ART initiation criteria have helped to increase coverage while decreasing the cost of treatment per child [18].

Although drug costs have declined, they remain high relative to adult formulations, in part because of the size and location of the market. With the total number of HIV-infected children less than 15 years old at only approximately 10% of the total number of people living with HIV globally, and pediatric ART coverage about half that of adult coverage, the market volume of ARVs for children is substantially smaller than that for adults [2]. Even with full implementation of WHO 2013 guidelines and universal coverage of all children under 5, children would still account for less than 10% of the global need for ART. Furthermore, as pediatric HIV is nearly eliminated in the first world, there is limited demand for pediatric ARVs in those markets. In sub-Saharan Africa, where 90% of pediatric HIV is found, purchasing power is low and most HIV services are dependent on external funding [19]. Moreover, because ARV formulations for children require multiple dosing and formulations dependent on weight and age of the child, the already small market is further fragmented. Given these market dynamics, it is not surprising that the preferred first-line ART regimen for children less than 3 years, consisting of abacavir/lamivudine and lopinavir/ritonavir (LPV/r) is more than three times the cost of preferred adult line regimens (based on CHAI reference ceiling price list). Table 1 summarizes the cost of the WHO pediatric regimens.

Table 1. Drug costs of WHO pediatric regimens.

ABC/3TC (60/30mg) FDC	\$168 ppy
LPV/r syrup	\$289 ppy
TDF/3TC/EFV (300/300/600 mg)	\$130.80 ppy

Source: Clinton Health Access Initiative (www.clintonhealthaccess.org). 3TC, lamivudine; ABC, abacavir; EFV, efavirenz; FDC, fixed-dose combination; ppy, per patient year; TDF, tenofovir.

In an effort to reduce drug costs and improve efficiency, the WHO Paediatric ARV Working group has developed guidance on dosing (aimed largely at pharmaceutical companies) for new and upcoming formulations (available at http://www.who.int/hiv/pub/meetingreports/paediatric_arv/en/index.html). The Interagency Task Team for the PMTCT (IATT) developed guidelines that promote an abridged, optimized list of essential pediatric ARVs, with a focus on fixed-dose regimens and dispersible tablets (i.e., dissolvable in liquid; available at http://www.who.int/hiv/pub/meetingreports/paediatric_working_group/en/index.html).

Since 2005, these efforts have contributed to the development of five dual and four triple generic pediatric fixed-dose combinations in solid and dispersible forms. Further efficiencies may be found through pooled procurement, in which multiple countries band together to purchase bulk quantities of pediatric ARVs allowing for more favorable pricing. The UNITAID program has championed this approach and currently accounts for up to 93% of generic ARV purchases, with the Global Fund accounting for up to 74% of 'innovator' purchases, or purchases from companies that hold the patent for the drugs and tend to sell at higher prices than generic pharmaceutical companies.

With these collective efforts and the increasing scale-up of pediatric treatment programs, prices for all pediatric ARV formulations will continue to drop, with fixed-dose combinations becoming increasingly less expensive than liquid formulations [17]. Although the pediatric ART formulary is far from optimal, the push for the manufacturing of essential pediatric formulations continues, as does the push to meld divided markets for larger pediatric commodity purchases.

Drug failure and resistance

Infants infected that were exposed to ARVs to prevent mother-to-child transmission will likely have multiple resistance mutations [19], with NNRTI resistance-associated substitutions particularly common and problematic given most countries' reliance on NNRTI-based first-line ART; with expanding PMTCT coverage, this will become more common. Although WHO guidelines recommend a protease inhibitor (LPV/r) as the backbone of pediatric ART first-line regimens, some national guidelines have yet to account for this, resulting in less optimal first-line ARV regimens and poorer outcomes

[20]. As an increasing number of children and adolescents continue treatment, resistance rates are steadily rising, with resistance rates among adolescents being especially concerning [21].

Resistance, selected for by both PMTCT exposure and increasing numbers of patients on long-term care, may necessitate third-line and fourth-line regimens, even in resource-poor settings. As pediatric cohorts age, not only will systems for comprehensive, longitudinal care need to be developed to maximize adherence and thus preserve ARV efficacy, but the associated increase in costs will also have to be managed [4].

Laboratory monitoring

The 2013 WHO guidelines call for increased availability of viral load monitoring. This development should improve ART outcomes for children and adults in resource-limited countries [22]. Increasing the availability of monitoring will raise costs, but the net impact on budgets is unclear, as improved treatment outcomes such as reduced resistance, may lead to cost savings elsewhere in the program. To better understand the costs implications, additional data on pediatric services are required to evaluate both the cost and effectiveness of existing and emerging laboratory monitoring strategies.

The possibility of point-of-care viral load testing and monitoring is of particular interest for children's programming. Synergizing pediatric and adult virologic testing needs, with quantitative (treatment monitoring) and qualitative (able to be used for EID) testing on the same platform has substantial utility from multiple perspectives. Without cost data, the net impact on budgets is difficult to predict, although simply having qualitative HIV RNA PCR capability would allow replacing current EID algorithms with likely substantial positive impacts on total cost.

Case finding and retention

Virologic testing for early infant diagnosis

The current strategy for identifying children infected with HIV and enrolling them into clinical care is programmatically more difficult and costly than that for adults. Scaling-up EID is expensive compared with antibody-based diagnostic strategies used in adult populations. Moreover, program costs and outcomes depend on factors such as the proportion of HIV-exposed infants undergoing EID testing; operational efficacy of the EID program in generating and communicating test results; and linkages of HIV-infected infants to care and treatment [23]. In some settings, such as South Africa,

EID and early ART have been shown to generate considerable cost savings. When more children are diagnosed in early stages [24,25], treatment can be more effective and costs associated with caring for children with advanced progression, can be avoided [23]. With recent evidence that very EID and treatment may allow for a functional cure, there is likely to be increased interest in strategies to identify the virus in the first days of life [26].

Postinfancy case finding

Active case finding of children after infancy proffers significant costs to pediatric programs in terms of money spent and years of life lost. After 12–18 months, older infants and children can be identified with less expensive antibody tests, but case finding strategies require coverage at multiple entry points including immunization clinics, sick child clinics, and for children being admitted to hospital. Such expansive coverage is costly, and research is needed to determine which approaches are cost-effective. Currently, no standard data on cost exist to help make these decisions. Although expanding provider-initiated testing and counseling at immunization clinics seems attractive, testing all children presenting for their first or second immunization visit will be expensive and may not yield many additional cases, particularly in low-prevalence settings. However, with some strategic thinking, examples of high-risk pediatric populations wherein yield might be higher and thus provide a more favorable argument for focusing resources include testing children admitted to hospital, orphans and vulnerable children program enrollees, and siblings of those enrolled in pediatric treatment programs. Postinfancy case finding is a clear area in which PMTCT investments can pay dividends in terms of reduced numbers of children requiring these services.

Retention in care

A substantial but poorly understood contributor to costs and effectiveness of pediatric HIV programming are activities that promote retention in care. Although it is a good assumption that poor linkage and retention as evidenced by loss-to-follow-up (LTFU) rates adversely impacts mortality in HIV-infected children [27], and is known to be higher in children prior to ART initiation than once a child is on ART [28], we are less certain of the costs associated with or generated by children who are not linked to care or who are LTFU. LTFU affects mortality estimates within programs, with an analysis of more than 8000 children in southern Africa calculating a two-fold increase in mortality at program level when LTFU taken into account [29], and a recently published model projecting as high as four-fold to five-fold underestimates in mortality in some programs when LTFU is not accounted for [30]. Mortality projections underpin much about overall programmatic cost-effectiveness, and understanding more about strategies to reduce LTFU and how they can be scaled is highly relevant. Depending on their cost, interventions directed at preventing LTFU in resource-limited settings, such as a broadly applied

community adherence support approach in South Africa utilizing patient advocates which has demonstrated effectiveness in this regard [31], have been projected to both improve survival and be cost-effective [32], and deserve consideration as programs grapple with setting priorities in today's cost-conscious environment.

Protocol for timing of treatment initiation

In contrast to previous guidance recommending universal treatment for all HIV-infected children under 2 years, the 2013 version of the guidelines calls for universal treatment of all children under the age of 5 and further simplifies clinical and immunologic initiation criteria for older children. This will add an estimated 770 000 new children to the existing 1.4 million in need of treatment over the next several years [3]. This will obviously increase the amount spent on treatment; if all these children were found and put on treatment, drug costs alone could top 200 million USD/year. It will, however, likely also increase program effectiveness, leaving the net impact on cost-effectiveness unclear. Moreover, it will likely reduce, or at least delay, the provision of high-level care for children in advanced stages, which would lead to cost savings. While on the one hand, then, expansion of treatment may bring cost-benefits in some programmatic areas, on the other hand it will increase costs in some areas, such as by increasing the number of children in need of second-line therapy [20]. Next steps include generating projections of resources needed, given this aspirational goal of finding and placing all these children on treatment.

Human resources for program implementation

The WHO as well as national governments in many settings encourages task shifting in ART programs due to scarce human resources, particularly physicians [33]. Task shifting reduces the costs of care in the short-term, but its impact on long-term costs is less clear [33]. Long-term costs will be in part determined by the quality of treatment. If treatment standards drop with task shifting and resistance increases, costs could rise. The good treatment outcomes and cost-effectiveness noted from task shifting ART management of stable patients to nurses in some settings [33,34], including for HIV-infected children [35], needs cost-effectiveness data for specific clinical outcomes from pediatric settings. Of particular interest would be pediatric data along the lines of that from a comparative study in South Africa of care delivered by physicians at a referral hospital treatment-initiation site versus care delivered by primary healthcare nurses at a primary health clinic [33]. In this study, nurse-directed

outcomes in adults were as good as or better than physicians' while overall costs of care were 11% less, despite patients being allowed closer follow-up (every 2 months of visits with nurses as compared with every 6 months with physicians), reflecting the much lower fixed and unit costs per visit at the primary health site.

Costing resources

The most accurate way to estimate the cost of a pediatric treatment program would be to do a comprehensive bottoms-up facility level costing exercise in which all costs associated with the intervention are identified and collectively added. However, the resources required to do this type of costing at a national scale are daunting and are often simply not available, often resulting in adaptation of costing information from adult or other programming. Because costing information cannot be simply transposed from one program to another, making assumptions about homogeneity of costs can be misleading and decrease the accuracy; mathematical models must be constructed to incorporate site-specific variables, which tend to be greater when costing pediatric programs due to unique challenges of pediatric care, the need for age-specific treatment, and other factors. Such models rely on informed but imperfect assumptions, and more variables and assumptions means less accuracy. For these reasons, top-down, model-based pediatric treatment costing methods provide but a crude, financial snapshot, in contrast to the case in adults in which treatment is more streamlined and there is considerably more financial stake in the number of persons ultimately in need of treatment. Several costing model resources are included in Table 2.

One of the recommendations from a 2006 WHO-sponsored workshop on HIV program approaches to costing was to produce a more generic HIV costing manual [36]. To assist the standardization of facility

costing, enabling comparisons to be made across facilities in a country, or even between countries, a Manual for Costing HIV Facilities and Services and an accompanying Workbook for Collection of Cost Information of HIV Services were therefore produced. This manual was intended to improve the standardization of facility costing, enabling comparisons to be made across facilities in a country, or even between countries, and has been widely used in developing country settings.

The Clinton Health Access Initiative (CHAI) first developed such a model, called the PMTCT and Peds Impact and Costing Model to look at the impact of the 2010 WHO ART guidelines on pediatric HIV and PMTCT costs. It has been recently updated (v3.0) to look at the 2013 WHO ART guidelines. It includes drugs, laboratories, human resources, shipping, and other operational guidelines (pmtctpedsmode@clintonhealthaccess.org).

Conclusion

Over the last decade, unprecedented cooperation and support among donor nations, the international aid community and the most severely affected nations, have led to substantial resources being directed to the HIV and AIDS response. With these resources, tremendous gains in the global response to HIV and AIDS have been made. Early efforts were focused primarily on adults with proportionately fewer resources directed to children. There are signs that this is now changing and the success seen with bringing to scale high quality adult care and treatment programming has started to expand to pediatric programming as well. Although pediatric treatment still lags behind, improvements in quality and coverage of PMTCT services mean that fewer children have been infected, and the number looks set to continue to fall. The global community can see a time in the not too distant

Table 2. Costing tools currently in use.

Selected costing tools The OneHealth Tool	The OneHealth Tool is a model to be used for supporting the costing, budgeting, financing, and national strategies development of the health sector in developing countries with a focus on integrated planning and strengthening health systems. This model seeks to leverage the most useful components of the different tools that currently exist and is designed in a modular fashion allowing for program-specific costing as well as health system component costing. http://www.futuresinstitute.org/software.aspx
WHO AMDS Toolbox	WHO AMDS Toolbox is composite collection of a wide range of tools to support procurement and supply management of HIV/AIDS commodities. http://www.psmtoolbox.org/en/index.php
Quantimed MSH tool	Quantimed MSH tool serves as a resource for quantification and forecasting. http://www.emtct-iatt.org/wp-content/uploads/2013/02/Quantimed-Pharmaceutical-Quantification-and-Cost-Estimation-Tool.pdf
JSI Pipeline Tool Access Pipeline	JSI Pipeline Tool Access Pipeline is for the creation and management supply plans following quantification. Pipeline incorporates stock on hand, orders in process compared to the demand shown in quantifications, and forecasts to facilitate the management of orders to meet the demand in timely manner without overwhelming warehousing and distribution infrastructure. http://deliver.jsi.com/dhome/resources/publications/softwaremanuals
PMTCT and Pediatrics Impact and Costing Model	PMTCT and Pediatrics Impact and Costing Model is developed by the Clinton Health Access Initiative (CHAI), and built in Microsoft Excel; the model is used to estimate the cost of PMTCT and pediatric programs, and to model impact, including estimates of HIV transmission from mother to child and the number of pediatric HIV infections averted. Contact: pmtctpedsmode@clintonhealthaccess.org .

future when pediatric HIV will be an uncommon event, even in the hardest hit countries.

With the release of the 2013 WHO guidelines, we are witness to bold policy expanding the eligibility of children for HIV treatment, and improvements of such treatment. This shift, however, comes at a time when we also see a tightening of donor funding and a call for increasing efficiencies in order to make fewer donor dollars go further.

There are humanitarian, equity, and child rights arguments as to why, even in highly resource-constrained settings, access to pediatric treatment must be increased. The resource constraints cannot, however, be ignored. Pediatric treatment for HIV must aim to be as cost-effective as possible. This article has highlighted a number of aspects of pediatric programs that drive cost but are potentially modifiable by policy makers and program designers, leading to more efficient resource allocation. Suggestions for improving efficiency in pediatric HIV programming (priority should be given to community-level interventions supporting the following suggestions and target for immediate scale-up, given known potential for impact and return on investment) are as follows:

- (1) Continue to develop and scale up child-friendly ARV formulations aligned to 2013 WHO pediatric treatment guidelines.
- (2) Continue to simplify pediatric HIV treatment protocols, aligning toward goals of placing pediatric HIV management into maternal-child health settings in primary health settings.
- (3) Improve access to community adherence support (target for immediate scale-up, given known potential for impact and return on investment).
- (4) Bulk ARV forecasting and purchasing, including regionally among countries.
- (5) Scale up early and active case finding, especially with high-risk populations (target for immediate scale-up, given known potential for impact and return on investment).
- (6) Prioritize retention in care, including scaling up proven best practices in this regard.
- (7) Improve access to virologic monitoring (target for immediate scale-up, given known potential for impact and return on investment).
- (8) Improve efficiency in PMTCT programming, including pushing the elimination of mother to child HIV transmission agenda.

Of course in many cases, community-level interventions are particularly likely to improve both pediatric HIV's cost-effectiveness and impact, and these should be prioritized.

In the global HIV sphere's resource-constrained environment, we must acknowledge that progress comes at a cost.

It is unlikely that making pediatric HIV treatment available to every child in need can be paid for by efficiency-based savings, as was the case earlier in the HIV response, when there was ample room for cost reductions in many programmatic areas. We may well have to spend more than we currently do – directed to interventions known to deliver disproportional returns, such as retention, case finding, and monitoring strategies. However, this should be money well spent, and result in the decreases in morbidity and mortality that the Global Plan seeks.

As is often the case with studies that seek to support policy, we end with a call for more research. There is a long way to go to increase coverage of pediatric treatment, and in looking for additional answers, we should start with continuing to define which interventions deliver the most return. As treatment improves and children live longer, new problems with aging cohorts will arise. Cost data are required to inform the design and management of interventions; moreover, context matters, which requires that the same data be collected in different settings. As described above, a number of costing tools have been developed to support such work.

Without more data on the costs and effectiveness of alternative approaches to pediatric HIV treatment, and careful planning and implementation, many children will be left outside the door, their fate sealed for the worse, and not by necessity.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS) (2011). Countdown to zero: Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110609_jc2137_global-plan-elimination-hiv-children_en.pdf. [Accessed 10 September 2013]

2. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS Report on the Global AIDS Epidemic. 2012. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_with_annexes_en.pdf. [Accessed 10 September 2013]
3. UNAIDS Global Plan Progress Report 2013. Accessed online 10 August 2013 at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130625_progress_global_plan_en.pdf
4. Abrams EJ, Simonds RJ, Modi S, Rivadeneira E, Vaz P, Kankasa C, *et al*. **PEPFAR scale-up of pediatric HIV services: innovations, achievements, and challenges.** *J Acquir Immune Defic Syndr* 2012; **60** (Suppl3):S105–S112.
5. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. **Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis.** *Lancet* 2004; **364**:1236–1243.
6. Kates J, Wexler A, Lief E, Gobet B (2011) Financing the response to AIDS in low- and middle-income countries: international assistance from donor governments in 2011. Accessed online 1 July 2013 at: <http://www.kff.org/hivaids/upload/7347-08.pdf>
7. 6th Stocktaking Report on Children and AIDS (Oct 2013). <http://www.childrenandaids.org/newsletter/sixth-stocktaking-report-to-be-launched-october-2013>. [Accessed 10 September 2013]
8. MacMillan AS, Simkiss D. **The United Nations Convention on the Rights of the Child and HIV/AIDS.** *J Trop Pediatr* 2009; **55**:71–72. doi: 10.1093/tropej/fmp024.
9. Menzies NA, Berruti AA, Berzon R, Filler S, Ferris R, Ellerbrock T, Blandford JM. **The cost of providing comprehensive HIV treatment in PEPFAR-supported programs.** *AIDS* 2011; **25**: 1753–1760.
10. Larson BA, Bii M, Henly-Thomas S, McCoy K, Sawe F, Shaffer D, Rosen S. **ART treatment costs and retention in care in Kenya: a cohort study in three rural outpatient clinics.** *J Int AIDS Soc* 2013; **16**:18026.
11. Orlando S, Marazzi MC, Mancinelli S, Liotta G, Ceffa S, Giglio P, *et al*. **Cost-effectiveness of using HAART in prevention of mother-to-child transmission in the DREAM-Project Malawi.** *J Acquir Immune Defic Syndr* 2010; **55**:631–634.
12. IATT FEWG Regional Costing Workshop Report. 30 November 2012. <http://www.emtct-iatt.org/wp-content/uploads/2012/12/FEWG-eMTC-Plan-Cost-Projections-Meeting-Report-30-November-20121.pdf>. [Accessed 10 September 2013]
13. Menzies NA, Berruti AA, Blandford JM. **The determinants of HIV treatment costs in resource-limited settings.** *PLoS One* 2012; **7**:e48726.
14. Scott CA, Iyer H, Bwalya DL, McCoy K, Meyer-Rath G, Moyo C, Rosen S. **Retention in care and outpatient costs for children receiving antiretroviral therapy in Zambia: a retrospective cohort analysis.** *PLoS One* 2013; **8**:e67910.
15. Meyer-Rath G, Brennan A, Long L, Ndibongo B, Technau K, Moultrie H, *et al*. **Cost and outcomes of paediatric antiretroviral treatment in South Africa.** *AIDS* 2013; **27**:243–250.
16. Holmes CB, Blandford JM, Sangrujee N, Stewart SR, DuBois A, Smith TR, *et al*. **PEPFAR's past and future efforts to cut costs, improve efficiency, and increase the impact of global HIV programs.** *Health Aff* 2012; **31**:1553–1560.
17. Waning B, Diedrichsen E, Jambert E, Bärnighausen T, Li Y, Pouw M, Moon S. **The global pediatric antiretroviral market: analyses of product availability and utilization reveal challenges for development of pediatric formulations and HIV/AIDS treatment in children.** *BMC Pediatr* 2010; **10**:74.
18. World Health Organization Paediatric HIV Guidelines. 2013. http://www.who.int/hiv/pub/paediatric/paediatric_arv_dosing.pdf. [Accessed 10 September 2013]
19. Palumbo P, Lindsey JC, Hughes MD, Cotton MF, Bobat R, Meyers T, *et al*. **Antiretroviral treatment for children with peripartum nevirapine exposure.** *NEJM* 2010; **363**:1510–1520.
20. Orrell C, Levison J, Ciaranello A, Bekker LG, Kuritzkes DR, Freedberg KA, Wood R. **Resistance in pediatric patients experiencing virologic failure with first- and second-line antiretroviral therapy.** *Pediatr Inf Dis J* 2013; **32**:644–647.
21. Wallis C. High levels of HIV-1 drug resistance in South African adolescents failing antiretroviral treatment. International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies. 4–8 June 2013, Toronto, Canada.
22. Walensky RP, Ciaranello AL, Park J, Freedberg KA. **Cost-effectiveness of laboratory monitoring in sub-Saharan Africa: a review of the current literature.** *Clin Infect Dis* 2010; **51**: 85–92.
23. Ciaranello AL, Park J, Ramirez-Avila L, Freedberg KA, Walensky R, Leroy V. **Early infant HIV-1 diagnosis programs in resource-limited settings: opportunities for improved outcomes and more cost-effective interventions.** *BMC Med* 2011; **9**:59.
24. Meyer-Rath G, Violari A, Cotton M, Ndibongo B, Brenna A, Long L, *et al*. **THLBB103: the cost of early vs. deferred paediatric antiretroviral treatment in South Africa – a comparative economic analysis of the first year of the CHER trial.** International AIDS Society. Vienna, Austria; 2010 [<http://pag.aids2010.org/Abstracts.aspx?SID=644&AID=178231>].
25. Binagwaho A, Mugwaneza P, Irakoze AA, Nsanzimana S, Agboniyitor M, Nutt CT, *et al*. **Scaling up early infant diagnosis of HIV in Rwanda, 2008–2010.** *J Public Health Policy* 2013; **34**:2–16.
26. Lilian RR, Kalk E, Technau KG, Sherman GG. **Birth diagnosis of HIV infection on infants to reduce infant mortality and monitor for elimination of mother-to-child transmission.** *Pediatr Infect Dis J* 2013 [Epub ahead of print].
27. Brinkhof MW, Pujades-Rodriguez M, Egger M. **Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and metaanalysis.** *PLoS One* 2009; **4**:e5790.
28. Okomo U, Togun T, Oko F, Peterson K, Jaye A. **Mortality and loss to programme before antiretroviral therapy among HIV-infected children eligible for treatment in The Gambia, West Africa.** *AIDS Res Ther* 2012; **9**:28.
29. Fenner L, Brinkhof MW, Keiser O, Weigel R, Cornell M, Moultrie H, Davies MA. **Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa.** *J Acquir Immune Defic Syndr* 2010; **54**:524–532.
30. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, *et al*. **Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa.** *PLoS Med* 2011; **8**:e1000390.
31. Grimwood A, Fatti G, Mothibi E, Malahlela M, Shea J, Eley B. **Community adherence support improves programme retention in children on antiretroviral treatment: a multicentre cohort study in South Africa.** *J Int AIDS Soc* 2012; **15**:17381.
32. Losina E, Toure H, Uhler LM, Anglaret X, Paltiel AD, Balestre E, *et al*. **Cost-effectiveness of preventing loss to follow-up in HIV treatment programs: a Cote d'Ivoire appraisal.** *PLoS Med* 2009; **6**:e1000173.
33. Long L, Brennan A, Fox MP, Ndibongo B, Jaffray I, Sanne I, Rosen S. **Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort.** *PLoS Med* 2011; **8**:e1001055.
34. Sanne I, Orrell C, Fox MP, Conradie F, Ipe P, Zeinecker J, *et al*. **Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised noninferiority trial.** *Lancet* 2010; **376**:33–40.
35. Monyatsi G, Mullan P, Phelps B, Tolle MA, Machine EM, Gennari FF, *et al*. **Comparing HIV management by nurse prescribers to that of physicians at a paediatric centre in Gaborone, Botswana.** *S Afr Med J* 2011; **102**:34–37.
36. Beck EJ, Santas XM, Delay PR. **Why and how to monitor the cost and evaluate the cost-effectiveness of HIV services in countries.** *AIDS* 2008; **22** (Suppl 1):S75–S85.