Modelling the long-term impacts on affected children of adult HIV: benefits, challenges and a possible approach

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We outline the benefits, challenges and possible approaches to developing mathematical models that could be used to estimate the magnitude of negative consequences of adult HIV infection for children. Adult HIV infection can lead to numerous negative consequences for dependent children, including depression, anxiety, withdrawal from school and early sexual debut, among others. For advocacy and planning purposes, it is important to highlight and consider as many of these as possible. A focus solely on orphan numbers, which is the typical summary measure for children affected by HIV and AIDS, can be misleading. The complexity of child development that is characterized by the interaction of a multitude of proximal and distal factors, coupled with a significant lack of data on child development in the context of adult HIV infection make the development of models a challenging task. Although it may not be possible in the first attempt to develop a population-based model capable of examining family dynamics, the negative consequences together with the impact of interventions, steps in that direction can be taken. We propose approaches and assumptions that we believe will allow the development of a useful first set of models. We conclude with a brief discussion of the type of data that, if collected, would facilitate refinement and development of these models.

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Introduction

Adult HIV infection can lead to a range of negative consequences for affected children. A child will experience a direct consequence if they are infected through vertical transmission. This will, however, become an increasingly rare event with continued improvement in the coverage and quality of prevention of mother-to-child transmission interventions. Although the risks of infection are falling, there remain numerous indirect pathways linking adult HIV infection to negative consequences for children [1]. Parents or other caregivers may become preoccupied by their diagnosis and not be as attentive to the needs of their children. When seriously ill, they may be physically less able to provide care. When adult members are unable to work because of poor health or death, an affected family's income may decline, potentially leading to reduced spending on children, including on nutrition and education. When children are required to provide care or to supplement household income, they may be withdrawn from school. Following the death of a parent, children are often moved. The care

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they receive in their new home is at times substandard or even abusive. Sherr *et al.* [1], in this issue, provide a review of the growing evidence of these indirect consequences. They describe how adult HIV increases the risks children face and how in many instances children's physical and mental health, education and safety suffer as a result.

The substantial literature that has emerged in the last 10 years reflects the extent to which our understanding of the indirect consequences for children of adult HIV has deepened [1]. The field is however nascent, particularly relative to other topics in child development, such as the study of the implications of parent death or divorce, or childhood malnutrition. We have long-term longitudinal follow-up data on people who experienced these childhood adversities that allow us to examine long-term consequences. Although they do not look specifically at children affected by HIV and AIDS, these studies do include children who experienced similar difficulties. Stein *et al.* [2], also in this issue, consider what insights from the broader child development field are transferable to the study of children affected by HIV and AIDS, with a particular focus on the long-term consequences. They identify a range of consequences stemming from experiences that are similar in some ways to the experiences of children affected by HIV and AIDS, including negative physical and mental health effects, fewer years of completed education and lower future earnings. They note that typically these manifest in a highly affected minority; most children do not experience long-term consequences as a result of a given adversity.

The number of children orphaned as a result of AIDS is the most commonly reported summary measure of the impact of HIV and AIDS on affected children. As a summary statistic, orphan numbers can be misleading. First, it excludes children who are living with an infected parent. If that parent is symptomatic, children are at a greater risk of a range of negative consequences than they would have been in the absence of HIV [1]. When adults are able to access appropriate treatment, risks for dependent children are reduced, but not eliminated. Second, reporting orphan numbers ignores the significant variation in conditions of children meeting the definition of orphan. Many orphaned children will, with the support of their families and others, recover from the experience of adult illness and death, while a subpopulation will not cope and will suffer numerous and long-lasting negative consequences [1,2]. Third, the orphan figure only includes those who are still under 18 years of age. This implies that once an affected child becomes an adult, the impact is over; they are no longer included in the count. For the most affected children, the negative consequences will continue throughout their lives [2].

In this study, we discuss the potential benefits, and challenges, of developing mathematical models that would provide an estimate of a range of negative consequences of adult HIV infection for dependent children. Such models could potentially provide figures to replace, or supplement, the narrow and potentially misleading orphan numbers. Moreover, they could aid in prioritizing between alternative interventions. There are numerous challenges to developing such models, not least of which is the substantial amount of data required. We outline the challenges, and the approaches to developing models that we believe may be a useful first step on the road to overcoming such challenges, what questions might be asked of these models, and finally, what data collection strategies may help generate the kind of data that these models require.

The benefits of a model of the impact of adult HIV and AIDS on children

The benefits of building a model to provide estimates of the impacts of adult HIV and AIDS on children stem primarily from two sources: improved advocacy and improved prioritization. A model that provides estimates of a range of consequences, rather than only orphan numbers, would provide a fuller and more informative picture of the nature and magnitude of impacts that affected children experience. A model that estimates long-term outcomes, particularly those related to public health and economic outcomes, would highlight links to other sectors within, and external to, the HIV and AIDS response. For example, estimating the population level increase in risky sexual behaviour associated with being affected by HIV, and its implications for HIV incidence, would highlight links to HIV prevention.

From a planning perspective, a model of the consequences of adult infection on dependent children could assist in prioritization. The risks children face are the result of a complex interplay of proximal and distal factors, including parent health, family resources and the availability of services [1]. Different interventions target different factors. A model that captures the interactions will help identify which interventions, or a combination of interventions, will likely have the most desirable impact on the outcomes of interest. Although we may not be able to develop a model capable of fully evaluating interventions with the first effort, it remains a worthy goal.

The Brooking's Institute's Social Genome Project provides an example of the potential benefits of modelling long-term outcomes associated with children's experience [3]. They have developed, and are refining, a model that estimates the chances of American working class children reaching middle class, by adulthood. Long-term socio-economic outcomes are similarly a result of a complex interplay of factors. To the extent the Project has been able to capture these interactions, their model

provides an opportunity to examine different types of intervention across a range of common outcomes. For example, addressing childhood poverty can be examined alongside investments in primary education, both in terms of their impact on adult outcomes, such as earnings. Such direct comparisons allow for more informed priority setting.

The challenges of building a model to estimate the impact of adult HIV and AIDS on children

The two most significant challenges to building such a model relate to the complexity of child development and the limitations of the data that are currently available. Stein *et al.* [2] describe how, in child development, one of the few certainties is that there are few certainties. The consequence of a given childhood experience will depend on the context in which it is experienced, the characteristics of the child who experiences it, the wider support networks and the chronicity of the experience, to name a few. A model that seeks to predict child outcomes associated with adult HIV and AIDS must consider how risks of each negative consequence of interest differ according to various aspects of context and child characteristics. The challenge is to identify which contextual factors are central, and then to access data which allow risks associated with different combinations of these factors to be estimated.

The data on children affected by HIV and AIDS which are currently available are limited in ways that frustrate attempts to use such data to calibrate models. The long-term cohort studies that there are [4,5], are based in high-income countries, although useful sources of data for modelling the impact in these contexts, the data are less likely to be appropriate for calibrating models estimating impacts for low and middle-income contexts. The few cohort studies in low and middle-income countries cover narrow time bands and their sample sizes are a constraint. They are not large enough to allow the investigation of multiple interactions. With multiple factors playing a role in determining risk, there is an unavoidable rapid proliferation of combinations in any realistic model of HIV-affected children.

A further constraint is the way in which the analysis of these data is typically conducted and reported. For a single outcome, the distribution is important but often not reported. For example, it is unclear whether elevated depression is because many HIV-affected children are somewhat depressed, or a few are very depressed. Moreover, authors often examine one outcome at a time. We are interested if it is the same children experiencing multiple impacts.

An approach to building a model to estimate the impact of adult HIV and AIDS on children

No 'one size fits all' model is likely to serve across investigations of diverse impact pathways, such as investigations of likely experience of depression and abuse, early sexual debut or dropping out of school, but there are numerous common reusable threads and ideas that appear to capture the essence of the dynamics usually meant to be covered under the term 'HIV-affected children'. We outline a proposed modelling framework that covers a spectrum of useful models. On the simplistic end of this spectrum are heuristic models that can be deployed easily with little data, and on the complex (if not readily implementable) end are models that, given enough data, could potentially provide quantitatively realistic projections which are useful for supporting policy choices.

Models, of the type we are discussing, are defined by the following:

(1) Actors, such as parent and children;
(2) Environmental factors, such as rates of disease progression, access to care/treatment;
(3) States in which actors can be found (such as infected/ill/treated/dead);
(4) Events that change the states of actors;
(5) Rates at which possible events occur;
(6) Interactions between actors, captured as dependencies of the rates of events affecting one actor, on the states of other actors.

The complexity of the models is largely determined by which actors, environmental factors, states of actors, events and interactions between them are included, and the computational/analytical approach applied.

Analytical approach

In principle, there is considerable scope for developing differential equation models of the usual population dynamic type, which is widespread in economic, demographic and epidemiological scenario modelling, but there appears to be very limited scope for developing completely analytically tractable models beyond the most simple demonstration models. This is essentially because all the most important rates which necessarily arise are fundamentally time/age dependent.

The proliferation of possible states of adult/child pairs and the permutations of potentially unique transition rates may be easier to capture computationally in an individual level event simulation approach than in a model with an inordinate number of compartments or time dimensions (calendar time, times of early events that affect distributions of times of later events and so on). Individual

simulation, however, brings its own challenges of computational complexity. Also, as repeats of simulations are used to obtain mean outcomes, there needs to be ad-hoc testing for convergence of the summary statistics emerging from simulations, substantially complicating the procedure for running the model, and the need to pay attention to convergence of emergent mean indicators.

An important recommendation we make at this point is that effort be applied to developing models of 'cohorts' rather than 'populations'. By 'population' model, we mean a scenario in which the passing of calendar time brings about changes in occupation of the possible states of the system actors, who are of various ages, risk categories and so on. A cohort, by contrast, offers substantial simplification, by capturing an ensemble of life-trajectories without attempting to embed births and other events into a 'realistic' demographic and epidemiological context. This provides a reduction in complexity of calibration and scenario definition, but retains the capacity to investigate questions such as given a distribution of disease progression patterns among HIV-positive women, what proportion of schooling time is expected to be lost among their children, relative to a cohort of HIV-free mothers. This is far less ambitious than asking questions such as between 2010 and 2020, what is the distribution of times spent in school among learners in South African schools. Although the latter may be of considerable interest, we argue that answers of this level of specific quantitative realism are, and will for some time remain, well beyond the reach of achievable models.

Actors: mother–child dyads and the direction of impact

In principle, the welfare of children and parents affect each other, to some extent, in all directions, but the dominant effect is the conditions of parents affecting the outcomes for children, so we propose, as alluded above, to independently model the patterns of maternal/parental HIV disease progression and to shelve, for the time being, the question of how childrearing and early adverse effects experience by children, affects the wellbeing of their parents.

Parents in principle each affect the child, and also each other, but we propose initially focusing on models of maternal welfare in isolation of paternal states as a further simplification that seems necessary in light of the paucity of data.

Figure 1 demonstrates a basic model of parental (mother) disease progression. The disease transition rates are time (age) dependent, and this is intended to include, in principle, inter-dependencies of events, for example that the rate of accessing treatment is linked to time of onset of symptoms, and, of course, not just age. In keeping with the cohort (versus 'whole population') limitation that we proposed, we doubt there is much prospect, in the near term, of modelling the impact on children of a fully developed realistic, context-specific, ensemble of disease-progressing parents with nuances such as calendar time dependence of programmatic effectiveness.

States: mothers' health

The diversity of disease progression outcomes presents a challenge. Some HIV-infected mothers will experience rapidly deteriorating health, whereas others maintain relatively good health for a long time, and those who do experience ill health will have a wide range of experiences with treatment access and efficacy. Hence, questions about the average outcome for children raise the question of what is the average experience of HIV-infected parents, which itself is changing and difficult to assess. Modellers may wish to start by considering a realistic hypothetical mother timeline, and explore what pressures and likely consequences this implies for children. Only once this appears to be modelled with some realism does it become feasible to ask about the average child experience taking into account the range of clinical trajectories of parents. At this stage, we are still talking about a hypothetical cohort. To elevate the discussion to the level of simulating an actual population in principle requires not just that a fully fledged mix of clinical

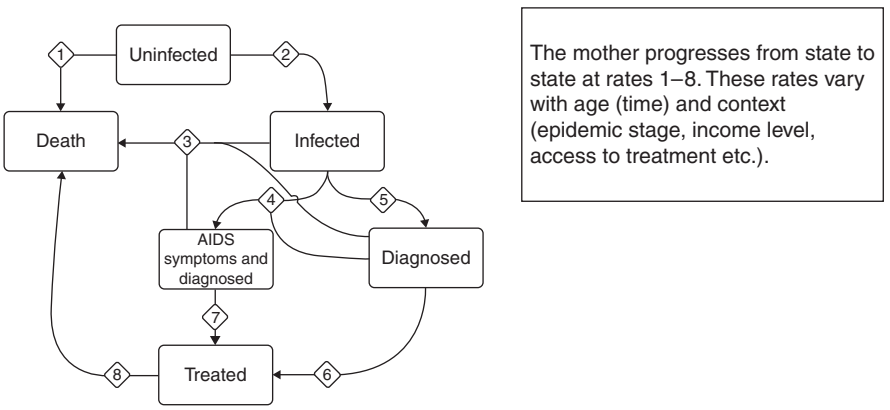

Fig. 1. Mother model.

outcomes is provided as an input to the model, but also that this is adapted realistically as the accessibility and quality of treatment evolves, and as incidence changes.

Linking states to events: mothers' health to child outcomes

Linking maternal state to child outcomes requires two steps. The first is the development of models for each child outcome; the second is to allow the rules/rates in these child outcome models to be sensitive to maternal state, and other relevant environmental factors. Figure 2 provides examples of the first step: Fig. 2a demonstrates a simple model that could serve as a starting point of investigations of school attendance. If outcomes are likely to cluster, such as with depression and abuse, and subsequent sexual risk behaviour, the influence of one outcome on the likelihood of the other can be incorporated, Fig. 2b outlines this example.

Given the proposed unidirectional influence of parents on children in these models, execution of the parent model, crucially incorporating fertility and age-dependent incidence (two nontrivial challenges), provides a distribution of contextual/environmental factors in which children's life trajectories can be modelled. We can isolate logically independent models of the primary relevant pathways of child development, and regard the parental state as a time-dependent environmental factor that in principle affects all dynamic rules/rates. Effectively, all the rates of movement from one state to another in Fig. 2 would be determined by the health state of the mother, as described in Fig. 1. In the schooling example for instance, maternal health changes over time and is independent of the child state. The child can leave school through graduation, death or drop out at the rates indicated, all of which depend on time (age) and, critically, the state of the mother. If we include only the health states alive or dead, there are already nine time-dependent parameters, that is nine functions of time that need to be estimated and supplied as inputs. Depending on how time variation is captured, this can lead to dozens of parameters. Further layers can be added to the model by allowing rates to vary according to contextual factors, such as if the mother's illness is occurring in the context of poverty or not, or if the child is male or female. Doing so, however, multiplies the data requirements further.

In summary, a scenario model of the form we are proposing proceeds in the following steps, which involve many technical details that we have glossed over:

(1) Selection of a hypothetical maternal HIV-infection progression pathway, or ensemble of pathways, which defines a cohort of mothers. This requires specification

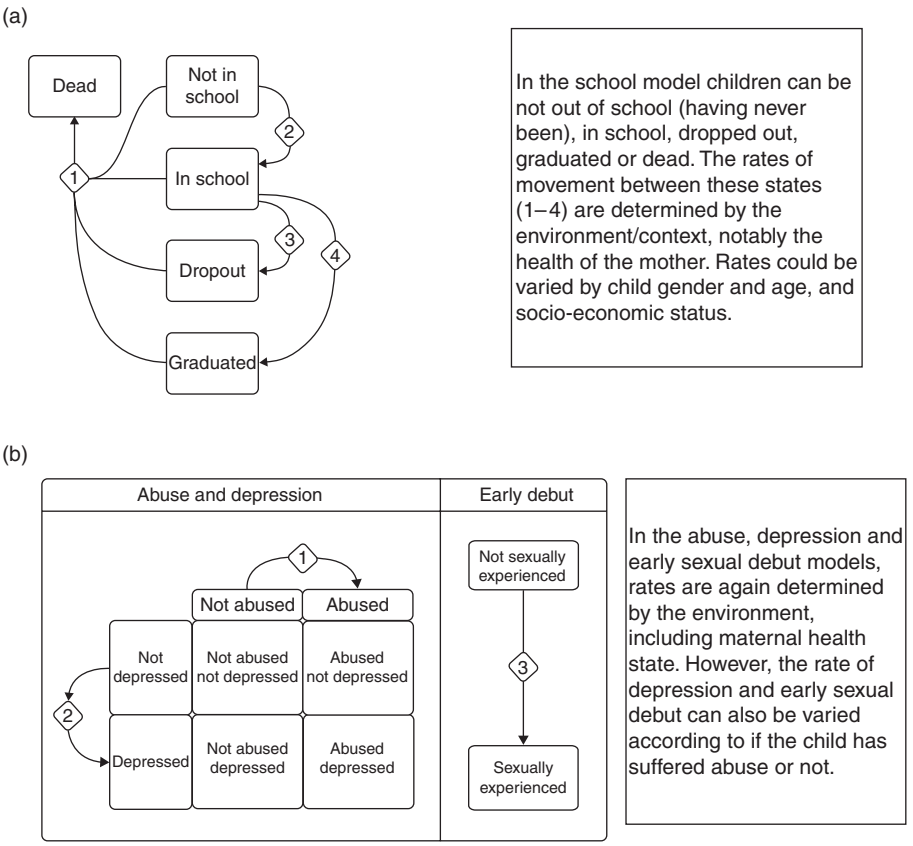

Fig. 2. Child outcome models: (a) School model. (b) Depression, abuse and sexual debut model.

of age of infection, or age-dependent incidence, and a distribution for waiting times to the health-changing events of Fig. 1.
(2) Addition of assumptions about fertility, possibly as a function of age, maternal HIV stage and parity, thus defining the cohort of children whose pathways are being investigated.
(3) Selection of child pathways, including parameters capturing rates, potentially as functions of child and maternal age and all maternal states.
(4) Performance of sensibly selected model runs, providing informative comparisons such as proxies for status quo, and counterfactuals lacking existing, or having additional interventions.
(5) Collation and interpretation of summary data indicating dependencies of outcomes on contextual factors.

Once constructed, a model with the above structure could be used to address many different study questions. One example is an investigation of how maternal mortality and morbidity affect schooling. We would need sufficient knowledge of fertility, incidence and survival, to capture the distribution of adverse maternal states during the adolescence of their children, when school dropout becomes a serious risk. Appropriate construction of a base scenario, and alternatives in which mothers have, for example, more access to treatment, should permit meaningful demonstration of increased mean time spent in school, or reduced numbers of children leaving school prematurely. Understanding contextual variation in fertility and age structure of incidence, and the level of background school dropout, should shed light on whether pressure on schooling is largely evenly spread or characterized by specific combinations of parameters suggesting the need for targeted interventions. With sufficient data on temporal trends, one could even frame expectations about the duration of transient phases before the possible emergence of a substantial restoration of 'normal' schooling patterns in an initially AIDS disrupted scenario.

Quantifying more complex pathways such as children experiencing neglect or abuse, hence adverse mental health such as depression, and hence increased vulnerability to high-risk behaviours may not be possible without some controversy. However, even a heuristic face-value plausible model may be instructive in terms of demonstrating the long-term feedback that is being experienced by the current cohort of young adults in the context of parental HIV. Alternatively, on a positive note, it is worth understanding the potential deepening of longer term positive impacts that can realistically be expected to follow from modest shorter term successes.

Development of useful and interpretable scenarios will always be a challenge, both because of data limitations and because of the complexity of the system and challenge of distilling out the right comparison of scenarios that offer meaningful insights into interactions of factors, likely time scales of impacts, and sensitivity of impacts to potential intervention, or sensitivity of predictions to parameter estimates. Early investigations are unlikely to yield strong direct system insights, but are already generating insights into the needs of data sets and potential studies, which are prerequisites to forming realistic views of the problem and rational planning of interventions.

Strategies for collecting appropriate data

Ideally, we would have long-term follow-up data on children affected by HIV and AIDS from high prevalence contexts, which better explains the causal pathways and the associated long-term implications of being affected by HIV and AIDS, in these contexts. Currently, the field is reliant primarily on cross-sectional data, as there are only a small number of cohort studies. With cross-sectional studies, it is difficult to identify impacts on children associated with adult infection. Negative outcomes may correlate with HIV, but not be caused by it; they may both be caused by some other factor such as drug-use. Introducing controls for potential confounders can lead to underestimates of impact if HIV acts through what is now being controlled for, poverty for example. It is similarly difficult to control for the possibility of reverse causality when examining potential pathways to impact. A child may be moved because they have behavioural problems, or may have behavioural problems because they were moved. Moreover, currently, there are too few studies to allow discussions of how broader socio-economic contexts may be shaping consequences for children. Longitudinal studies with large sample sizes conducted in different contexts will require significant and long-term commitment from donors.

Longitudinal studies will help, but given the complexity of the mechanisms linking adult infection to child outcomes, they will not necessarily allow a full examination of the pathways to impact. To begin to isolate different pathways, it will be important to include intervention studies. Interventions that target (disrupt) a particular pathway, if they are shown to be successful, speak to the part played by that pathway. For example, if it is thought that child depression results from either the experience of adult illness or economic pressures, household income could be protected with cash transfers, and the results compared with a control group. The model could then be expanded to include different rates of depression in contexts in which income is protected.

Conclusion

Modelling the long-term implications for children of adult HIV is near impossible. The complexity of child development and the hefty data requirements are major

challenges. The difficulty is, however, not reason enough to shrink from the task. Building a model of this type will focus attention on what we do and do not know about the implications of adult HIV for children, and in doing so, it will highlight gaps in the current data. Results, even if highly sensitive to critical assumptions, will help advocacy efforts draw attention away from the narrow conception of the issues that stems from a focus on orphan numbers. Similarly, it will bring out the potential links to other aspects of the response to HIV and AIDS. Finally, in time, such a model could help inform which combinations of interventions, targeting different aspects of the context in which negative consequences occur, should be at the core of our response. Although not all benefits will be reaped from the first attempt, efforts are underway, by the authors and supported by USAIDS/PEPFAR, to develop appropriate models, and results will be become available during 2014.

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Conflicts of interest

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