WORKING
PAPER

A Technical Supplement: Reducing the Burden of HIV/AIDS in Infants

The Contribution of Improved Diagnostics

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HEALTH

PREFACE

This working paper contains technical material supporting the article by Aledort et. al. "Reducing the burden of HIV/AIDS in infants: the contribution of improved diagnostics" *Nature* S1; 19-28 (2006). It is intended to be read in conjunction with that article. This supplement includes additional material referred to in the published article as well as secondary analyses and tables that were not included in the published paper. Although this technical supplement in its current form has not been formally peer-reviewed, an earlier version of this paper, which also contained material that appears in the corresponding *Nature* paper, was reviewed by two outside experts and was revised in response to their comments.

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A. OVERVIEW

The dearth of available diagnostic tests for human immunodeficiency virus (HIV) that can be used in resource-poor areas is a major barrier to the provision of effective care and the treatment of HIV-infected infants.. Consequently, there is an urgent need for alternative strategies and biomarkers for early diagnosis of HIV infection in infants. In light of the enormous burden of HIV/AIDS on children in developing countries, as well as the need for better diagnostic tests, we developed a model to quantify the potential health benefits associated with a hypothetical new test for the early diagnosis of HIV infection in infants aged <12 months. We focused on sub-Saharan Africa, where ~90% of all children with HIV infection reside[1]. The analysis considers test-performance characteristics and access requirements associated with a new diagnostic, as well as the availability of antiretroviral therapy (ART).

B. METHODS

B.1 Modeling Health Outcomes and Treatment Harm

We considered several different health outcomes for each diagnostic pathway in the model, including life-years (LYs) saved, disability-adjusted life years (DALYs) saved, and the proportion of total disease burden averted with alternative new diagnostic tests. Whereas for acute and/or generally curable conditions, lives saved may be the most appropriate outcome, for HIV/AIDS, this is not the case. First, some infants and children live with AIDS as a chronic condition into adolescence and beyond, but experts agree that in resource-poor countries, even HIV-infected infants who are treated with ART are unlikely to live a full life span. Therefore counting individual lives conditional on surviving AIDS is less informative than counting the fraction of life-years saved. Second, we estimated DALYs to account for the fact that infants living with HIV/AIDS do not live their remaining years in perfect health. DALYs are a measure of morbidity due to a given conditions. To estimate DALYs, we multiplied disability-adjusted weights for HIV and for AIDS from the Global Burden of Disease[2] study by our calculation of LYs. We

also elected to track the number of scarce ART regimens saved with a new diagnostic compared to the status quo as an indicator of economic benefit. After all health outcomes were assigned and quantified, we aggregated outcomes across the access levels to estimate health outcomes associated with the status quo.

Each of these outcomes includes the potential negative effects associated with treatment ("harm of treatment"). Treatment harm might arise from the inappropriate use of scare resources. For example, when an ART regimen is used to treat an infant with a false positive test for HIV infection, an HIV-infected infant is consequently denied treatment, and life-years are lost. Moreover, treatment harm may be associated with the development of antiviral resistance, adverse effects of ART, and stigma associated with HIV treatment. Note that if there were no penalty associated with treatment, it would be optimal to simply treat all individuals (regardless of disease status). In the estimation of treatment harm, we therefore explicitly assume that treatment harm will cause loss of life at some point. Additional details of the modeling approach and the estimation of the harm associated with treatment are provided in Girosi et al.[3] and the corresponding technical supplement.

B.2. Additional Data Inputs and Assumptions

Due to a dearth of available data on the distribution of HIV-infected infants by clinical stage, we defined this distribution deterministically using expert opinion and the observation that most infants under the age of one year who die of AIDS or an AIDS-related event are likely to have clinical stage III or IV disease. Moreover, we assumed for simplicity that clinical staging following the IMCI/HIV algorithm or the new diagnostic was *independent* of test characteristics and prevalence of disease.

Since there are limited opportunities for testing, diagnosis and treatment of HIV infection in infants and HIV progresses rapidly in this population, we assumed that untreated HIV-infected infants with stage I/II disease had health outcomes similar to untreated HIV-

infected infants with stage III/IV disease (i.e., disease progresses rapidly from stage I/II to stage III/IV in untreated infants such that outcomes are the same.)

Finally, we assumed that HIV infected infants were twice as likely to be symptomatic as asymptomatic, i.e., two-thirds HIV infected infants are in the symptomatic/access to IMCI/HIV algorithm branch and one third are in the asymptomatic/no access to IMCI/HIV algorithm branch. This assumption influences our estimates of prevalence, which were calculated as follows:

$$prev\_Symptomatic\_IMCI = \frac{\frac{2}{3}\cdot p}{p\_Sympt\cdot(1-p)+\frac{2}{3}\cdot p},$$

$$prev\_Asymptomaic\_noIMCI = \frac{\frac{1}{3}\cdot p}{(1-p\_Sympt)\cdot(1-p)+\frac{1}{3}\cdot p}$$

where p = population prevalence of HIV infection.

C. Additional Model Calibration Details

Prior to evaluating the potential impact of a new test for early diagnosis of HIV in infants, we explored the predictive validity of the model. First, we obtained estimates of the number of AIDS-related deaths from the WHO World Health Report and the Global Burden of Disease study. Since we were unable to identify these figures for our target population of infants less than one year, we calibrated the model against cross-sectional regional estimates of AIDS-related mortality for children less than 5 years, which represented the best available data. Sources suggest that in sub-Saharan Africa in 2002, 285,000-314,995 children under the age of 5 died from AIDS or AIDS-related events.[2, 4]

Since the model was not designed to count AIDS-related mortality, for calibration purposes, we re-populated the model with estimates of 2 to 5 -year cumulative mortality

rates for treated and untreated HIV-infected infants from the published literature.[5-7] We then used the status quo model to compute the number of treated and untreated HIV/AIDS cases in each access category and multiplied by the appropriate cumulative mortality rate. Table 1 provides the set of parameter values used in the calibration model.

Table 1. Parameter Values Used in Calibration Model

Parameter	**Sub Saharan Africa**
Population & Prevalence	
Number of births in 2005*	39,994,000
Prevalence of HIV in children aged 0 to 5†	2.25%
Cumulative 5-Year Mortality in Children Aged 0-5	
HIV-infected infants treated with ART	0%
Untreated HIV-infected infants[6, 8]	63%
HIV-uninfected infants[6]	0%

* Number of births is taken as the 2005 medium variant for sub-Saharan African countries from the UN World Population Prospectus found at http://esa.un.org/unpp/index.asp?panel=2

† HIV prevalence is calculated as the product of MTC transmission and maternal HIV seroprevalence..

Assuming a relatively stable epidemic, our model predicted 435,649 deaths over a one-year period due to HIV/AIDS in Sub-Saharan Africa in children under the age of five. There are several possible explanations as to why our model overestimated AIDS-related deaths. First, there are some limitations associated with the data against which we calibrated: They are based mainly on autopsy data, they are slightly dated, and they are cross-sectional, all of which may bias the estimate downward. Second, our model may have overestimated the number of deaths since we did not consider the effect of co-trimoxazole (CTX) prophylaxis on overall survival in HIV-infected children in the calibration exercise. Third, our method of calibration which uses births from the year 2005 and relies on cumulative mortality rates to determine the number of those children who will die of HIV/AIDS before the age of 5, may bias our estimates upwards.

In order to provide the reader with a sense of how the different model parameters affect the predicted number of status quo childhood deaths, we have implemented the calibration procedure in Excel. In the interactive Excel spreadsheet "HIV Parameter Validation_Africa.xls" users can vary the input parameters used in the model to see how these changes affect the calibration.

D. SECONDARY ANALYSIS

In Aledort et al.[9] we report the potential health impact of a hypothetical new test for the early diagnosis of HIV infection when all infants who test positive by the IMCI/HIV algorithm or the new diagnostic are assumed to be eligible to receive ART, irrespective of clinical stage of disease. However, following the current WHO treatment guidelines, we explored a more realistic scenario in which the provision of ART is conditional on disease stage III/IV (i.e., only infants who test positive by the IMCI/HIV algorithm are eligible to receive ART).

D.1. ART is Conditional on Clinical Staging

Results for this secondary analysis are presented in Table 2. Each numbered row corresponds to a particular potential new diagnostic defined by sensitivity, specificity, infrastructure requirements (moderate, minimal and zero infrastructure), and ART availability (5, 50 and 100 percent). We report health outcomes associated with the new test in terms of LYs, DALYs, and ART regimens saved for a one-year period. The numbers in italics under each outcome are standard deviations that quantify uncertainty around the estimate.

The results in Table 2 suggests that barriers associated with clinical staging and scarce ART significantly restrict the potential contribution of a new test for early detection of HIV in infants. In this analysis, although all infants who are IMCI/HIV algorithm "Positive" are assumed to receive CTX prophylaxis (i.e., irrespective of clinical stage), in order for infants to receive ART, they must (1) have access to care, (2) be sick enough to

present to an IMCI provider, (3) receive a positive test by the IMCI/HIV algorithm *and* (4) be classified as stage III/IV. In order to isolate the effect of a new diagnostic, we assume that as in the status quo, ART remains conditional on clinical staging and that it is available at the same sequential levels (5, 50, 100 percent) as in the status quo. When the new test is introduced, however, access to testing is no longer limited to infants who are sick and have access to an IMCI provider; rather, healthy infants are now also eligible for HIV screening.

An important health benefit of a new HIV diagnostic tool is the potential to diagnose and treat symptomatic and asymptomatic infants. The results in Table 2 indicate that important health gains are realized with a new diagnostic tool that can be used in health settings such as immunization sites that require minimal or zero infrastructure (e.g., portable or bench-top test to be performed by a low-level nurse, and without water, electricity or external reagent requirements). When all barriers to ART and to clinical care for asymptomatic infants and infants formerly without access to an IMCI provider are removed, the full potential of a new diagnostic tool used in conjunction with clinical staging is readily apparent. Given the base-case prevalence of HIV in infants in sub-Saharan Africa, and the population of infants aged 0 to 1, a perfectly sensitive and specific test that is universally accessible (i.e. requires no infrastructure), can save 3,442,419 adjusted life years when ART availability is 100 percent.

We explored the potential health impact of a new diagnostic that has *inferior* performance characteristics compared to the IMCI/HIV algorithm (data not shown), and we found no associated improvement in health outcomes for any level of infrastructure or ART availability. This phenomenon can be partially explained by the high harm of treatment. For example, the model suggests that the "costs" in terms of life-years associated with deployment of a non-specific test outweigh the "benefits" of a new test with minimal or zero infrastructure requirements that can reach more infants. Similarly, with a test that is less sensitive than the status quo IMCI guidelines, enough HIV-infected infants are missed such that the loss of life-years outweighs the potential benefit associated with wider access. Although we did not present the full range of

sensitivity/specificity combinations in Table 2, it may be the case that if a new test is specific enough, it can have very low sensitivity and still generate net benefits, conditional on wider access compared to the status quo.

Table 2. Incremental Adjusted LYs, DALYs and ART Regimens Saved when ART is Conditional on Clinical Staging

	Test	Sensitivity (%)	Specificity (%)	Adjusted LYs Saved† (*SD*)	Adjusted DALYs Saved† (*SD*)	ART Regimens Saved‡ (*SD*)
Status Quo: *IMCI HIV Pediatric Guidelines*		70	80			
Moderate Infrastructure *(Access to IMCI-trained provider for Clinic-Based Test for Symptomatic Infants Only)***§**						
5% ARV Availability for all Clinical Stages						
1	More Specific Test	70	90	25,431	0	25,431
				(7,567)	*(8,683)*	*(4,757)*
2	More Sensitive Test	90	80	37,178	37,379	0
				(24,258)	*(34,235)*	*(4,796)*
3	Overall Better Test	90	90	62,609	37,379	25,431
				(16,453)	*(22,202)*	*(7,148)*
4	Perfect Test	100	100	106,629	56,069	50,863
				(41,781)	*(33,876)*	*(5,281)*
50% ARV Availability for all Clinical Stages						
5	More Specific Test	70	90	254,313	0	254,313
				(113,954)	*(50,737)*	*(101,359)*
6	More Sensitive Test	90	80	242,995	256,719	0
				(141,473)	*(198,790)*	*(55,375)*
7	Overall Better Test	90	90	497,308	256,719	254,313
				(240,961)	*(181,163)*	*(49,870)*
8	Perfect Test	100	100	873,118	385,079	508,625
				(238,817)	*(211,975)*	*(66,419)*
100% ARV Availability for all Clinical Stages						
9	More Specific Test	70	90	508,625	0	508,625
				(151,461)	*(100,140)*	*(107,931)*
10	More Sensitive Test	90	80	471,682	500,430	0
				(193,050)	*(241,570)*	*(122,697)*
11	Overall Better Test	90	90	980,307	500,430	508,625
				(323,752)	*(216,420)*	*(188,529)*
12	Perfect Test	100	100	1,724,773	750,645	1,017,251
				(928,773)	*(901,133)*	*(126,566)*

Table 2. Continued

	Test	Sensitivity (%)	Specificity (%)	Adjusted LYs Saved† (*SD*)	Adjusted DALYs Saved† (*SD*)	ART Regimens Saved‡ (*SD*)
Status Quo: *IMCI HIV Pediatric Guidelines*		70	80			
Minimal Infrastructure *(Access to Test for Symptomatic and Asymptomatic Infants, e.g., immunization sites)*‖						
5% ARV Availability for all Clinical Stages						
13	More Specific Test	70	90	58,943	56,203	3,043
				(76,034)	*(20,462)*	*(11,559)*
14	More Sensitive Test	90	80	58,683	124,908	-65,551
				(93,839)	*(82,939)*	*(32,823)*
15	Overall Better Test	90	90	127,278	124,908	3,043
				(51,843)	*(77,731)*	*(15,632)*
16	Perfect Test	100	100	230,039	159,261	71,637
				(159,966)	*(113,010)*	*(13,345)*
50% ARV Availability for all Clinical Stages						
17	More Specific Test	70	90	395,796	385,999	30,432
				(172,085)	*(223,896)*	*(143,448)*
18	More Sensitive Test	90	80	342,247	361,576	0
				(268,280)	*(523,665)*	*(326,646)*
19	Overall Better Test	90	90	842,433	857,860	30,432
				(476,626)	*(596,755)*	*(251,305)*
20	Perfect Test	100	100	1,751,693	1,093,791	716,374
				(795,357)	*(849,834)*	*(77,673)*
100% ARV Availability for all Clinical Stages						
21	More Specific Test	70	90	770,077	752,438	60,865
				(279,092)	*(686,389)*	*(468,797)*
22	More Sensitive Test	90	80	664,340	704,831	0
				(544,251)	*(1,193,262)*	*(820,014)*
23	Overall Better Test	90	90	1,637,050	1,672,252	60,865
				(515,485)	*(660,060)*	*(435,048)*
24	Perfect Test	100	100	3,442,419	2,132,158	1,432,747
				(1,059,071)	*(1,045,752)*	*(225,222)*

Table 2. Continued

	Test	Sensitivity (%)	Specificity (%)	Adjusted LYs Saved† (*SD*)	Adjusted DALYs Saved† (*SD*)	ART Regimens Saved‡ (*SD*)
Status Quo: *IMCI HIV Pediatric Guidelines*		70	80			
No infrastructure *(Universal Access to Test for Symptomatic and Asymptomatic Infants)*¶						
5% ARV Availability for all Clinical Stages						
25	More Specific Test	70	90	74,683	94,459	-19,266
				(57,208)	*(77,060)*	*(30,759)*
26	More Sensitive Test	90	80	62,986	174,094	-110,170
				(157,195)	*(155,890)*	*(56,884)*
27	Overall Better Test	90	90	153,889	174,094	-19,266
				(74,302)	*(115,105)*	*(21,039)*
28	Perfect Test	100	100	284,395	213,912	71,637
				(112,926)	*(117,675)*	*(11,404)*
50% ARV Availability for all Clinical Stages						
29	More Specific Test	70	90	421,396	648,737	-192,661
				(324,445)	*(543,381)*	*(294,258)*
30	More Sensitive Test	90	80	342,247	361,576	0
				(537,820)	*(1,034,311)*	*(565,310)*
31	Overall Better Test	90	90	939,088	1,195,667	-192,661
				(498,998)	*(818,790)*	*(291,787)*
32	Perfect Test	100	100	2,106,968	1,469,132	716,374
				(862,178)	*(1,083,329)*	*(93,149)*
100% ARV Availability for all Clinical Stages						
33	More Specific Test	70	90	806,632	1,264,602	-385,322
				(470,580)	*(1,084,282)*	*(762,168)*
34	More Sensitive Test	90	80	664,340	704,831	0
				(522,704)	*(1,004,145)*	*(940,397)*
35	Overall Better Test	90	90	1,811,531	2,330,748	-385,322
				(1,191,533)	*(1,823,694)*	*(670,456)*
36	Perfect Test	100	100	4,132,049	2,863,821	1,432,747
				(1,674,235)	*(2,268,491)*	*(296,295)*

*Standard deviations are shown in parenthesis. ART, antiretroviral therapy; DALYs, disability-adjusted life years; HIV, human immunodeficiency virus; IMCI, Integrated Management of Childhood Illness; LYs, life years. †Life years and DALYs saved are adjusted to account for the harm associated with treatment and life years saved through reduction in overtreatment. Therefore, an adjusted life year saved is a composite measure reflecting life years saved through improvements in appropriate treatment, reduction in inappropriate treatments and the harm associated with treatment. Outcomes are for 1 year of full implementation of the proposed diagnostic and treatment policy. ‡ART regimens saved is a measure of the benefit associated with new tests that have better specificity than the status quo (that is, it accounts strictly for the gains from reducing unnecessary or inappropriate treatment). §Moderate infrastructure refers to access to an IMCI-trained provider for a clinic-based test for symptomatic infants only. A test can be performed in a setting with moderate infrastructure if electricity and water are available, and a laboratory is at least minimally equipped (for example, in African hospitals). Staff requirements include nurses, a physician and a technician with minimal training. ‖Minimal infrastructure refers to access to tests for symptomatic and asymptomatic infants (for example, immunization sites). A test can be performed in a setting with minimal infrastructure if it does not require water or electricity and is able to be performed at the clinic by an individual with minimal training.¶No infrastructure refers to settings with no reliable water or electricity, and makes no assumptions about the training or literacy of the caregiver. Here, we assume universal access to a test for symptomatic and asymptomatic infants. See Girosi and colleagues[3] for more detailed information on calculating the percentage of people with access to a new diagnostic requiring moderate, minimal or no infrastructure.

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