Is HIV Seroprevalence Declining Among Women who Access PMTCT Services? A Multi-Country Analysis.

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Rationale

Recent publications suggest that HIV prevalence may be declining in some settings (UNAIDS 2006). In SubSaharan Africa, where almost two thirds of all HIV infected persons live, there is some evidence that HIV prevalence is declining or at least stable in some countries (UNAIDS 2006). Specifically, the 2006 UNAIDS update summarizes recent research indicating declines in prevalence in Ethiopia, Kenya, Tanzania, and Zimbabwe and stabilization of the epidemic in Eritrea, Rwanda, Uganda, and West and Central African countries with available data. Additionally, there is evidence that prevalence may be declining in other settings. For example, Kumar *et al* (2006) reported decreases in seroprevalence among antenatal and STI clinic attendees from 2000 to 2004 in India. On the other hand, some have cautioned against concluding that seroprevalence is declining, given the heterogeneity of sub-epidemics in SubSaharan Africa (Asamoah-Odei, Garcia Calleja, and Boerma, 2004). Specifically, these authors conclude that only East Africa has experienced a decline in seroprevalence and that the epidemic may be stabilizing in other parts of the region.

The objective of this study is to determine the extent to which similar declines in seroprevalence may be observed among pregnant women who access prevention of mother to child transmission (PMTCT) programs based in antenatal care and labor and delivery services. The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) is one of the largest providers of PMTCT services in the world, supporting counseling and testing for pregnant women and antiretroviral prophylaxis for HIV positive pregnant women and HIV exposed infants in 18 countries. As of December 2006, EGPAF supported PMTCT services in over 1500 health care facilities in Cameroon, China, Cote d'Ivoire, Dominican Republic, Democratic Republic of the Congo, India, Kenya, Lesotho, Malawi,

Mozambique, Russia, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe.

The potential bias of using seroprevalence that is routinely reported in PMTCT program data to estimate HIV prevalence among antenatal care attendees and the general population have been described by Hladik *et al* (2005). These authors summarized comparisons between unlinked anonymous testing (UAT) based in antenatal care with PMTCT program results in Uganda, Thailand, Botswana, and Kenya to assess whether or not routine data reported from PMTCT programs should replace the UAT method. In countries such as Thailand, where ANC and PMTCT coverage is exceptionally high and routinely reported PMTCT data are complete and accurate, the authors conclude that PMTCT data can be used instead of UAT based in ANC to track HIV prevalence in the general population. On the other hand, in settings where routinely reported PMTCT data are of poor quality and prevalence ratios between those who accept and those who do not accept testing are not known, such as Kenya, the authors recommend maintenance of UAT as the most valid and reliable method for estimating HIV prevalence.

More specifically, Mpairwe *et al* (2005) compared prevalence estimates in a setting where UAT based in ANC may be biased by the introduction of PMTCT services. In their year long comparison of women who accept counseling and testing in the context of a PMTCT program at a large district hospital to those who refuse these services, they observe that pregnant women who accept testing during the first month that PMTCT services were offered were significantly more likely to be HIV positive than those who refused testing. In subsequent months, the difference between the two groups of women was neither clinically nor statistically significant, with the exception of those months when less than 70 percent of all antenatal care attendees accepted testing. Thus, the authors concluded that the introduction of PMTCT may result in biased estimates of seroprevalence measured through sentinel surveillance in the short term, as women who perceive themselves to be at high risk for HIV *and* are willing to be tested seek care at antenatal care clinics with PMTCT services, which may bias results from the UAT method if women choose a facility with PMTCT instead of the ANC facility that is part of the surveillance network. With these caveats, analysis of this program data is a unique opportunity to observe trends in seroprevalence in an important sub-population of

pregnant women accessing PMTCT services through the largest provider of such services in the world.

All EGPAF-affiliated PMTCT programs perform HIV testing in accordance with national policies for antenatal patients. Most facilities employ rapid HIV antibody testing utilizing *Determine HIV-1/2* (Abbott Laboratories, Abbott Park, Illinois), which has been donated without cost to many resource-limited countries, and most provide same-day results, improving the percentage of women who receive their test results (Malonza *et al*, 2003). In a minority of facilities, women return for a separate visit to learn their HIV serostatus. Most countries currently employ serial testing (Ginsburg, Miller, and Wilfert, 2006). National policies also determine whether nurses or other personnel in the antenatal care or labor and delivery areas can be trained and certified to perform the HIV test.

HIV testing is offered in the context of local HIV counseling and education and ARV prophylaxis guidelines. Many countries have recently transitioned or are in the process of transitioning to opt-out testing after utilizing opt-in approaches in the initial phase of PMTCT program implementation. Likewise, many EGPAF-supported programs have expanded services beyond antenatal care to include counseling and testing in labor and delivery settings. In terms of ARV prophylaxis for HIV positive pregnant women and HIV exposed infants, the majority of EGPAF-supported sites provide single dose nevirapine to women and infants; however, many sites are introducing and scaling up other multi-drug ARV regimens in antenatal care.

Data and Methods

Each country program submits quarterly or biannual facility-based summary data to EGPAF for review and analysis; data are cleaned at the country level and validated at headquarters. The data represent a cross section of women reached with counseling and testing services during the reporting period. Additionally, sites report on the number of HIV positive pregnant women identified, the number of HIV positive pregnant women receiving any type of ARV prophylaxis or treatment, and the number of HIV exposed infants provided with ARV prophylaxis. From the beginning of the program in 2000 through December 2006, more than 3 million pregnant women were counseled and 2.5 million tested in EGPAF-supported sites. Of those tested, just over 264,000 were found to be HIV positive. These data were exported to STATA for secondary analysis. Due to

data quality concerns observed during the start up period throughout the program, data from the first reporting period for each site was dropped from the analysis.

Analysis

For each site, quarterly or semi annual data were summed and an annual seroprevalence rate was calculated by dividing the total number of pregnant women with an HIV positive test by the total number of pregnant women tested. Site-years for which the total number of women tested were fewer than 30 were excluded from the analysis. In addition, the data was further cleaned by excluding site-years for which the calculated seroprevalences are zero or higher than 50 percent. This cutoff was chosen because prevalence higher than 50 percent has not been empirically shown elsewhere and is more likely to be due to poor data quality. The final data for analysis consist of 2392 site-years of data, which corresponds to 1257 sites.

Global trends in seroprevalence as well as site specific trends were assessed by fitting a random effect linear regression model of seroprevalence on the year of report. These trends are examined on the period from 2001 to 2006. A random effect model was chosen to control for repeat measurements on the same site. Because we are interested in general trends in seroprevalence, only random intercept models are fitted with fixed effect on the year of report variable as well as other control variables. Control variables used are the uptake of testing and the volume of services. The uptake of testing is calculated as the total number of pregnant women tested divided by the total number of eligible women (the sum of the number of first antenatal care visits and the number of women arriving in labor and delivery with unknown serostatus per year). This variable is included due to the association between uptake of testing and prevalence described in previous literature (Mpairwe *et al* 2005). The volume of services is the sum of the total number of first ANC visits and the total number of deliveries; this variable is a proxy for the type of facility, with the assumption that high volume sites are most likely to be tertiary hospitals and other referral facilities, while low volume sites are most likely primary health care centers or dispensaries.

The equation of random effect model is:

$$Y = \beta_0 + v + \beta_1 T + \beta_2 X_1 + \beta_3 X_2 + \beta_4 C + e$$

Where

Y is the annual seroprevalence,

T is the year of the report,

X_1 and X_2 are the uptake of testing and the volume of services (respectively),

v is the random effect, assumed to be normally distributed with mean 0 and a constant variance u,

e is the error term, also assumed to be normally distributed with mean 0 and a constant variance σ,

β_0, β_1, β_2 and β_3 are the regression coefficients; β_4 is a vector of regression coefficients for country dummy variables C. β_1 is the regression slope for the year of report and expresses the adjusted global trend in the seroprevalence. It represents the average increment change in the seroprevalence for one year change.

In addition to the model above, an interaction model was also fitted with an interaction term between the year of report and the country dummy variables in order to determine the unadjusted and adjusted country specific trends in seroprevalence.

Results

Program data from thirteen country programs and 1257 sites were included in the analysis. These are Cameroon, Cote d'Ivoire, DR Congo, Kenya, Malawi, Mozambique, Rwanda, South Africa, Swaziland, Uganda, Tanzania, Zambia, and Zimbabwe.
The period of time for which change in seroprevalence is estimated varies from two to five years, with Cameroon having first received EGPAF support in 2001 and Cote d'Ivoire in 2005. The number of sites contributing to the estimate for the first year of EGPAF support ranges from 3 in DR Congo to 51 in Tanzania; in December 2006, the range is 5 (Malawi) to 210 (Tanzania). In every country, average seroprevalence among women tested for HIV at EGPAF-supported sites has decreased since the initiation of EGPAF support. Malawi stands out in terms of the magnitude of decline in seroprevalence over time in the same sites, as the program added only one site over the course of the program through the end of 2006. Table 1 includes unadjusted seroprevalence estimates among pregnant women who were counseled and tested and the number of reporting sites for the first year of EGPAF support and as of December 2006 for each country.

Table 1. Unadjusted seroprevalence estimates for pregnant women tested for HIV at EGPAF supported PMTCT programs, by country

Country	First year of EGPAF support	First year of EGPAF support		December 2006	
		Seroprevalence	Number of sites	Seroprevalence	Number of sites
Cameroon	2001	9.4	12	8.1	202
Cote d'Ivoire	2005	8.3	29	7.8	67
DR Congo	2003	5.1	3	1.6	13
Kenya	2003	7.2	9	5.6	129
Malawi	2003	20.2	4	12.6	5
Mozambique	2005	15.3	9	13.5	13
Rwanda	2002	9.5	6	6.9	27
South Africa	2002	34.6	19	27.5	16
Swaziland	2004	42.3	3	36.2	18
Tanzania	2004	5.9	51	4.2	210
Uganda	2003	13.1	26	6.4	163
Zambia	2002	23.4	4	14.3	103
Zimbabwe	2003	23.3	25	17.6	150

Regression analysis

Table 2 presents coefficients and 95% confidence intervals for the regression of seroprevalence on the year of report, controlling for the country, the uptake of testing and the volume of services. The global trends in seroprevalence among pregnant women are indicated by the coefficient of the year of report. The results indicate an overall statistically significant downward trend in the seroprevalence over time. Adjusting for the country, the uptake of services and the volume of services at the site, the seroprevalence decreases annually by an average of 0.8 percentage point. The uptake of testing also indicates an interesting result consistent with the literature: higher uptake of HIV testing among pregnant women is significantly associated with lower seroprevalence.

Comparison of seroprevalence across countries is indicated by the country coefficients in Table 2. As expected, South Africa and Swaziland have the highest seroprevalence. Zimbabwe, Zambia, Mozambique and Malawi have significantly higher seroprevalence than Cameroon while Congo DR, Tanzania, and Kenya have significantly lower seroprevalence. No statitstical difference is observed between Cote d'Ivoire, Rwanda and Cameroon.

Table 2. Regression coefficients, 95% confidence interval, linear random effect regression of seroprevalence

Variable	Value (β)		95% Confidence interval	
Country				
Cameroon	Reference country			
Cote d'Ivoire	-0.63		-2.05	0.79
DR Congo	-6.67	***	-9.26	-4.08
Kenya	-1.99	***	-3.07	-0.91
Malawi	4.79	**	0.47	9.12

Mozambique	5.92	**	3.01	8.83
Rwanda	-1.23		-3.16	0.69
South Africa	21.33	***	19.81	22.86
Swaziland	29.65	***	27.22	32.07
Tanzania	-3.24	***	-4.18	-2.31
Uganda	-1.33	**	-2.35	-0.03
Zambia	6.95	***	5.77	8.14
Zimbabwe	9.96	***	8.89	11.04
Year of report	-0.80	***	-0.96	-0.65
Uptake of testing	-0.01	***	-0.02	-0.01
Overall R-square	0.65			
Number of observations	2381			

*** p<0.01; ** p<0.05, * p<0.10

The model also controls for the volume of services.

Table 3: Unadjusted and adjusted slope and its 95% confidence interval of the trends in seroprevalence by country

Country	**Unadjusted**		**95% CI**		**Adjusted**		**95% CI**	
Cameroon	-0.15		-0.46	0.15	-0.15		-0.45	0.14
Cote d'Ivoire	0.31		-1.40	2.01	0.32		-1.34	1.99
DR Congo	-0.91		-2.37	0.54	-0.99		-2.40	0.43
Kenya	-0.40	*	-0.85	0.05	-0.37		-0.82	0.08
Malawi	-1.66	**	-2.95	-0.37	-2.00	***	-3.40	-0.60
Mozambique	-1.99		-5.00	1.02	-0.85		-3.87	2.18
Rwanda	-0.32		-0.98	0.34	-0.48		-1.13	0.16
South Africa	-0.92	***	-1.52	-0.32	-0.84	***	-1.42	-0.26
Swaziland	-2.18	*	-4.59	0.23	-2.33	*	-4.68	0.02
Tanzania	-0.63	*	-1.27	0.01	-0.66	**	-1.29	-0.03
Uganda	-1.55	***	-1.99	-1.12	-1.55	***	-1.97	-1.13
Zambia	-1.42	***	-1.92	-0.91	-1.34	***	-1.84	-0.85
Zimbabwe	-1.64	***	-2.09	-1.18	-1.57	***	-2.01	-1.13

*** p<0.01; ** p<0.05, * p<0.10

The adjusted model is controlled for the uptake of testing and volume of services.

Table 3 presents the unadjusted and adjusted trends in seroprevalence by country. Consistent with Table 2, these results show a downward trend in all countries except in Cote d'Ivoire. The apparent positive trends in Cote d'Ivoire is probably related to data quality and to the fact the trends are observed only for 2005 and 2006. The unadjusted downward trends are significant in 8 out of the 12 countries. When these trends are adjusted for the uptake of HIV testing, they remain statistically significant in 7 countries. The marginal significant trends observed in the unadjusted model disappear in the adjusted model for Kenya. The steepest decline in the seroprevalence is observed in Swaziland and in Malawi with an average annual decline of 2 percentage points or more. Uganda, Zambia and Zimbabwe show an annual percentage decline of one or more

percentage points. Among the observed significant trends, seroprevalence in South Africa and Tanzania is decreasing at a slower rate than the other countries.

Comparison of EGPAF seroprevalence estimates to UNAIDS estimates

Table 4 includes seroprevalence estimates among pregnant women in major urban areas from the UNAIDS Epidemiological Fact Sheets for each country included in the analysis at two points in time corresponding to years preceding the beginning of EGPAF supported PMTCT (around 2000) and the most recent year available (range from 2002 – 2004). With the exception of Cote d'Ivoire, South Africa, and Swaziland, each country has reported a decline in seroprevalence since 2000. The observed trends among pregnant women tested for HIV at EGPAF-supported sites are consistent with these UNAIDS estimates (Table 4), except for the small decline in South Africa noted in the adjusted estimates and the comparatively steep decline in Swaziland. Thus, the results for Cote d'Ivoire may not be due to data quality or short duration of program implementation after all. In fact, UNAIDS estimates for pregnant women in all settings (urban areas and outside urban areas) decreased from 2004 to 2006 in Cote d'Ivoire.

In general, the consistency between the UNAIDS and EGPAF estimates is not too surprising, given that many EGPAF supported programs initially began in urban areas and have spread to other peri-urban and rural areas over time. Even where EGPAF has extended coverage of PMTCT services well beyond major urban areas, the large primary health centers and maternities in urban areas probably bias overall seroprevalence estimates downward, since the majority of pregnant women tested for HIV at EGPAF supported sites reside in urban, peri-urban, or secondary urban areas.

Table 4. Median HIV prevalence among pregnant women in major urban areas, by country, UNAIDS Epidemiological Fact Sheets

Country	**Survey dates**	**Year 1**	**Year 2**
Cameroon	2000, 2003	12	7
Cote d'Ivoire	2002, 2004	6.3	9.8
DR Congo	2000, 2004	4.1	3.8
Kenya	2000, 2004	15	10
Malawi	2001, 2004	20.1	18
Rwanda	2000, 2003	23	13.2
South Africa	2000, 2004	24.3	28
Swaziland	2000, 2004	32.3	40.3
Tanzania	2000, 2003	12.2	10
Uganda	2000, 2002	11.3	8
Zambia	2001, 2004	29.8	25.9

Zimbabwe	2000, 2004	31.1	19.7

Discussion

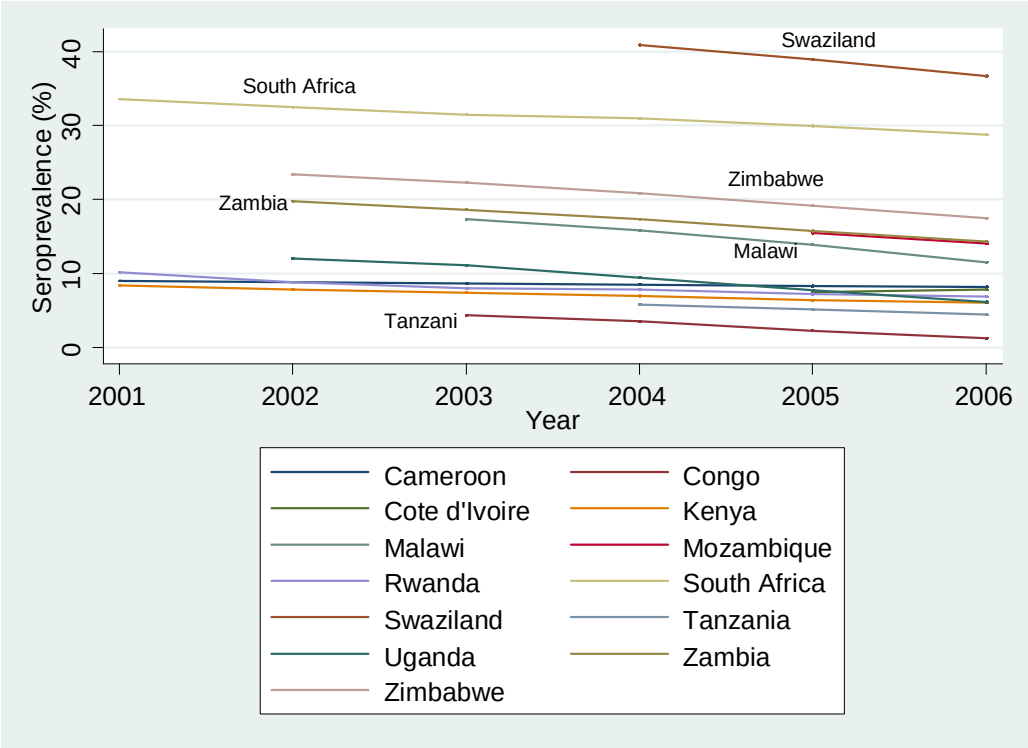
This analysis supports earlier conclusions regarding the decline in HIV seroprevalence in countries at the epicenter of the global HIV pandemic (UNAIDS 2006, Sheldon, Halperin, and Wilson 2006). These data are representative of a specific sub-population of pregnant women with access to PMTCT services offered in antenatal care and/or labor and delivery, thus conclusions regarding estimated decreases in prevalence can not be generalized to the larger population in each country. Likewise, the analysis supports earlier conclusions on the association between uptake of testing and seroprevalence, specifically, that seroprevalence among pregnant women is higher when uptake of testing is low. This may be due to the self selection of women particularly at risk for HIV who agree to be tested in settings where the opt-in strategy is implemented. Additionally, the analysis sheds light on future research questions and the potential need for key population characteristics to be included in routine PMTCT program data. For example, what additional data, if any, should PMTCT programs routinely collect in order to better ascertain program performance and better understand trends in seroprevalence among the target population?

Moreover, further research is needed to identify differences between women who access PMTCT services during the start up phase and those who access services after programs are well established. The observed decline may be due to the fact that women who know they are at risk for HIV infection actually seek antenatal care at facilities with PMTCT services, initially a small number of sites. As services rapidly scale up, fewer HIV positive women may be tested at one of the original sites as women who would have sought PMTCT there have other options closer to home. As Mpairwe *et al* (2005) point out, seroprevalence estimates may be biased at the introduction of PMTCT services in a given geographic area because women who know they are at risk will seek ANC at sites where they can receive a basic PMTCT package.

Lastly, these data point to a need for more rigorous assessment of the impact of counseling and testing services based within PMTCT programs as a primary prevention strategy. Does HIV counseling and education provided in the context of PMTCT programs really help HIV negative women remain negative? This is a question that

cannot be answered with program data alone. Further impact evaluation of PMTCT as a primary prevention strategy is a key activity to be undertaken to better understand the contribution of these activities to a country's overall HIV prevention programs. Such research could point to promising interventions that may be added to the basic package of PMTCT services to enhance this effect and strengthen models of service delivery in antenatal, labor and delivery, and postnatal care settings.

Graph w/seroprevalence estimates.



References

Asamoah-Odei E, Garcia Calleja JM, and Boerma T. 2004. "HIV prevalence and trends in sub-Saharan Africa: no decline and large subregional differences." *The Lancet.* 364 (9428): 35-40.

Ginsburg AS, Miller A, Wilfert CM. 2006. "Diagnosis of pediatric human immunodeficiency virus infection in resource-constrained settings." *Pediatric Infectious Disease Journal.* 25: 1057-1064.

Hladik W, Masupu K, Roels T, Tanarak P, Kaharuza F, Bunnell R, Seguy N, Marum L. 2005. "Prevention of mother-to-child transmission and voluntary counseling and testing programme data: what is their utility for HIV surveillance?" *AIDS.* 19 (Suppl 2): S19-S24.

Kumar R, Prabhat J, Arora P, Mony P, Bhatia P, Millson P, Dhingra N, Bhattacharya M, Remis RS, Nagelkerke N, ISHA Investigators. 2006. "Trends in HIV-1 in young adults in south India from 2000 to 2004: a prevalence study." *Lancet*. 367 (9517): 1164-72.

Malonza IM, Richardson BA, Kreiss JK, Bwayo JJ, Stewart GC. 2003. "The effect of rapid HIV-1 testing on uptake of perinatal HIV-1 interventions: a randomized clinical trial." *AIDS.* 17: 113-118.

Mpairwe H, Muhangi L, Namujju P, Kisitu A, Tumusiime A, Muwanga M, Whitworth J, Onyango S, Biryahwaho B, Elliot A. 2005. "HIV risk perception and prevalence in a program for prevention of mother-to-child transmission: Comparison of women who accept voluntary counseling and testing and those tested anonymously." *Journal of Acquired Immune Deficiency Syndrome.* 39 (3): 354-358.

Shelton J, Halperin DT, Wilson D. 2006. "Has global HIV incidence peaked?" *Lancet*. 367 (9517): 1120-2.

UNAIDS. 2006. "AIDS epidemic update: special report on HIV/AIDS." Geneva: World Health Organization.