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(Monica Magadi)

**Trends in under-five mortality in countries with high HIV prevalence:
When will they decline again?
With special reference to the Agincourt DSS**

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Abstract

With the diffusion of highly-active anti-retroviral therapies (HAART), the mortality of adults of both sexes started to decline again, after years of fast increase in African countries with high HIV prevalence, since about year 2005. However, this does not seem to be the case for under-five mortality, which continued to rise in the same countries. The study focuses on under-five mortality trends in six countries of Southern Africa where HIV prevalence among adults is higher than 20%. Data come from DHS surveys, supplemented with other data after 2005. Trends in under-five mortality are fitted with a linear-logistic regression model. Mortality increases are compared with trends in HIV seroprevalence among pregnant women. Two DSS sites located in South Africa are also analyzed: Agincourt and Hlabisa. Results show that no national survey has yet shown a significant decline in under-five mortality. However, in South Africa, vital registration systems indicate a decline since 2006, and DSS data show a decline at the same date in Agincourt, and even earlier in Hlabisa (2004). Mortality declines are linked to the rapid progress in preventing mother to child transmission of HIV and in treating children infected with HIV.

Key Words: Under-five Mortality; HIV/AIDS; HAART; Mother to child transmission; Sub-Saharan Africa; South-Africa; Agincourt.

Introduction

The health transition has been underway in the world for about a century, and even more in European countries and countries of European settlement. The health transition can be characterized by several mortality indicators (life expectancy at birth or at age 10, infant mortality, mortality of adults age 15-59, etc.), and best by mortality of young children, such as under-five mortality. In Africa, earliest evidence of mortality decline goes back to the early years of the colonial period, at least in countries where data are available, since little is known of mortality levels and trends prior to 1950. Numerous efforts of reconstructing under-five mortality trends since 1950 were conducted in the past 50 years, starting with the work conducted in the 1960's in the United States, in England, in France, in International organizations (United Nations Population Division, World Health Organization, World Bank), leading to numerous syntheses. [Brass et al. 1968; United Nations 1982; Mandjale 1985; Hill & Hill 1988; Hill 1991; Feachem & Jamison 1991] More recent work confirmed the overall favorable mortality trends in Africa, despite numerous accidents due to political crises, economic crises and emerging diseases [Ahmad et al. 2000, Garenne & Gakusi 2006]

The most important accident in the health transition in sub-Saharan Africa was the emergence of HIV/AIDS. This emerging disease became epidemic in the 1980's in many African countries, and by year 2005 a significant proportion of African populations was infected with the virus. The spread of the disease was uneven, with major differences by country, ranging from less than 1% in some places (as in Senegal), to 50% or more among young adults in other places (as in Kwazulu Natal province of South Africa). AIDS is one of the few infectious diseases which is almost always lethal under natural conditions (unless efficient treatment is applied), although the latency of the disease is long. The median duration between primo-infection and death is estimated roughly to be 10 years for adults, and somewhat less for children. As a consequence, large pockets of infections translate into major rise in mortality in general populations, but with a relatively long delay.

With respect to children, most of the transmission of the virus occurs from infected mother to child, although cases of iatrogenic transmission were also documented at the beginning of the epidemic. Mother to child transmission (MTCT) occurs during pregnancy, usually during the second and third trimester, during delivery, or after delivery through breastfeeding. In case of an infected mother, MTCT is not systematic, and occurs in about 30% of the cases (range 25% to 35%), depending on numerous factors, and in particular on

patterns of breastfeeding and mother's viral load. As a consequence, the under-five mortality impact of HIV infection among pregnant women is complex. In absolute terms, it depends primarily on the level of infection of the mothers, measured by the proportion of pregnant women who are HIV seropositive. In relative terms, it also depends on the underlying level of under-five mortality: the higher the baseline level, the lower the relative impact. Furthermore, the mortality impact also depends on the prevention of MTCT, as well as more recently on the treatment infected of children with Anti-Retro-Viral therapy (ARV).

The aim of this paper is to document recent cases of under-five mortality decline after a period of rise due to HIV/AIDS and to relate these new reversals to the prevention of MTCT and to ARV treatment among children. Since these are new phenomenon, we will rely on recent case studies, hoping that more data will become available soon. Before presenting data, methods and results, we provide a brief background on prevention and treatment of HIV among children.

Prevention and treatment of HIV among children

Many efforts were devoted to prevent mother to child transmission of HIV since the early days of the epidemic. These efforts dealt with the prevention of HIV transmission during pregnancy, delivery and breastfeeding. These policies changed over time between say 1990 and 2010 depending on drug availability and on scientific knowledge. Numerous clinical trials were conducted, leading sometimes to conflicting results, and to rapid changes in policies.

Obstetrics: First observations of HIV contamination during labor and delivery go back to the late 1980's. Infected women were then proposed to deliver by Caesarian-section. Elective C-section delivery (ECS) reduces somewhat the risk of transmission, but was never implemented on a large scale in Africa.

Anti-Retro-Viral drugs (ARV): Numerous drug regimens were tried to lower the viral load of infected mothers in order to reduce MTCT. The first drug was zidovudine (AZT), available since the late 1980's, which was used extensively in Africa only in the late 1990's and early 2000. Nevirapine (NVP) was found to have some efficacy in 1999, and was used extensively in many Southern-African countries, primarily because its cost was low. Stronger reductions in MTCT were obtained by combining several ARVs (bi- or tri-therapies). In particular, the combination of AZT+NVP was recommended by WHO in 2004 and became fashionable in many countries shortly afterwards. In the following years, various combinations were tried

with Lamivudine (3TC), such as AZT+NVP+3TC, or AZT+3TC, or combinations with other medicines such as Lopinavir (LPV) and Abacavir (ABC), with various successes. In any case, bi- or tri-therapies could reduce significantly MTCT, by 50% to 70% and could have major effects on under-five mortality.

Breastfeeding: Several strategies were tried to reduce or suppress HIV transmission through breastfeeding. WHO recommendations changed over the years, and were not necessarily followed by countries. In the early 1990s, the fashion was to continue breastfeeding, hoping that the gains from breastfeeding were higher than the losses from HIV infection. Later, it was considered better to use bottle feeding whenever the mother could afford it. After year 2000, several alternative strategies were tried: exclusive breastfeeding for only 5 months, and breastfeeding combined with ARV's (NVP or NVP+3TC).

Treatment of infected children: When tri-therapies became available and affordable for African countries around year 2005, infected children were also offered treatment. This seems to be an efficient way of reducing mortality, although precise studies are lacking to demonstrate an impact.

The full combination of all protective measures (tri-therapies, C-section, bottle feeding) could reduce MTCT by some 90%, leading to only 3% of transmission (range 2% to 4%), and combined with treatment of infected children could reduce AIDS mortality to almost zero. However, this full scale strategy has been implemented only recently, and on a limited scale.

For understanding mortality trends, it is almost impossible to have precise information on the policies that were implemented and to evaluate them accurately. Firstly, they changed overtime and rapidly, secondly their coverage is poorly documented, and thirdly their coverage seems to vary quickly in time as well as in space, some areas implementing them rapidly, while others did not, or did it much later. So that one could only scrutinize mortality trends and try to relate these trends with major changes in policies.

Data and Methods

For the analysis of changing under-five mortality trends in relation with HIV, several datasets were used: national surveys and local studies.

1) National data: DHS surveys and censuses

Demographic and Health Surveys (DHS) from 35 African countries were used for reconstructing under-five mortality trends up to the last year available, e.g. year 2005. The method of the reconstruction was presented elsewhere. [Garenne & Gakusi 2004] In brief, annual death rates were computed from maternity history data, and a trend was fitted with a linear-logistic regression. Changes in trends were tested, and only those significant at $P < 0.05$ were kept. The possible impact of HIV/AIDS on under-five mortality was calculated by applying a death rate to the proportion of infected children, using the UNAIDS mortality standard. [UNAIDS 2002] The proportion of infected children was calculated by multiplying the proportion of HIV seropositive pregnant women by a constant rate of MTCT. For Botswana, we also used the 2006 National Demographic Survey to supplement the last available DHS conducted in 1988. For South-Africa, we used data from the 2001 census and from the 2007 Community Survey to supplement data from the 1998 DHS survey. In South Africa, we also used published data from vital registration for the 1997-2008 period. Reconstructed data are available from the Ferdi web site. [Garenne, 2010]

2) Local data: DSS from Agincourt and Hlabisa

Two in-depth studies of local populations recently became available, both based on comprehensive Demographic Surveillance Systems (DSS): the Agincourt DSS (1992-2010) and the Hlabisa DSS (2000-2008), both located in rural areas of South Africa. Both sites were well documented elsewhere. [Tollman et al. 1997a & 1997b; Byass et al. 2010; Hosegood et al. 2004; Herbst et al. 2009; Ndirangu et al. 2010] In brief, the populations of a set of villages were studied by routine censuses and routine registration of births, deaths and migration, providing a full scale population register. In addition, causes of death were assessed by verbal autopsy. Both cover a population of about 90,000 persons, a sample size large enough to analyze even small changes in under-five deaths rates.

Results

1) National DHS surveys

Out of the 35 countries studied with DHS data, only 6 showed a major increase in under-five mortality due to HIV/AIDS, all of them in Southern Africa: South-Africa, Botswana, Zimbabwe, Namibia, Lesotho, and Swaziland. This was expected since these countries are not only the most infected with HIV/AIDS (seroprevalence > 20% among pregnant women in year 2000), but also countries where under-five mortality at baseline was the lowest (e.g. < 100 per 1000 in 1990). HIV/AIDS had an effect in other countries as well, but not to an extent where it produced a major rise in mortality: it simply slowed, or sometimes stopped the mortality decline for a while (e.g. Kenya, Cameroon, Zambia). But in these countries, mortality decline resumed in the most recent years mainly because the decrease in mortality from other causes exceeded the increase in HIV/AIDS mortality. Figure 1 summarizes mortality trends by country group. In all but Southern Africa mortality decline was continuous, hardly changed by emerging HIV. In Southern Africa, mortality increase was considerable, from an estimated 54 per 1000 in 1992 to an estimated 84 per 1000 in 2005 for the six countries combined.

2. Trends in Southern Africa from national surveys

The mortality increase due to HIV/AIDS was dramatic in each of the six southern African countries, leading to an average increase from lowest value to peak value of +39 per 1000 live births in under-five mortality. [Table 1] In South-Africa, $q(5)$ was estimated at 47 per 1000 in 1993 and 85 in 2006; in Zimbabwe, $q(5)$ was 61 per 1000 in 1987 and 85 in 2005; in Namibia and Botswana the impact was somewhat smaller (63 per 1000 in 1994 to 71 per 1000 in 2006; and 47 per 1000 in 1987 to 87 per 1000 in 2006); whereas in Lesotho and Swaziland the impact was even larger (85 per 1000 in 1985 to 126 per 1000 in 2009; and 48 per 1000 in 1991 to 139 per 1000 in 2007). By year 2007, Swaziland was close to the African average, whereas in 1991 it was one of three countries with the lowest under-five mortality. According to available national demographic surveys, none of these countries showed any decline in under-five mortality at time of the latest year available (2006 in South Africa; 2005 in Zimbabwe; 2007 in Namibia; 2006 in Botswana; 2009 in Lesotho; 2007 in Swaziland).

All these mortality increases are roughly consistent with estimated impacts of HIV prevalence among pregnant mothers, assuming lack of prevention and treatment up to 2005. If one discounts the expected effect of HIV, one obtains a prolongation of previous trends. Calculations of expected mortality impact based on seroprevalence among pregnant women indicate an increase of +56 per 1000 in under-five mortality. This compares with an estimated +63 per 1000 obtained by comparing estimates of $q(5)$ at peak mortality with previous trends prolonged to the same year. Given the uncertainty of all these values, the two estimates of the impact of HIV/AIDS on under-five mortality can be considered as equivalent. This shows that prior to 2005, the prevention of MTCT had a negligible impact on under-five mortality trends, and even up to 2008 in Lesotho.

3. Trends from vital registration of South Africa 1997-2008

A reversal in increasing mortality trend was found in vital registration data from South Africa. Published data cover children aged 0-9 years for the 1997-2008 period. [Stat-SA 2010] Results show a change in trends after 2006, corresponding with the implementation of bi-therapies and later tri-therapies to prevent MTCT. The decline in mortality is still modest (-6% in year 2008 compared with 2006), but clearly indicates a major change from previous increase between 1998 and 2006 (+66%). [Figure 2]

4) Trends in Agincourt 1992-2010

Agincourt is an isolated area, a former homeland, located near the Mozambican border. Although it is served by a network of nearby hospitals, the study area has only one public clinic, a few satellite clinics, and no full time physician. As a result, it seems that prevention of MTCT started relatively late, and had not reached full coverage yet by year 2010. Mortality data indicate a decline in under-five mortality from 1992 to 1996 ($P= 0.029$), then a rise from 1996 to 2006 ($P< 0.0001$), followed by a decline from 2006 to 2010 ($P= 0.024$). [Figure 2a] The changes in slopes from a period to the next were all highly significant ($P< 0.0001$). The pattern of change could be fitted with a third-degree polynomial. This model predicted a baseline value of 36 per 1000 in 1992, a bottom of 34 per 1000 in 1995, a peak of 69 per 1000 in 2006, and a lower value of 48 per 1000 in 2010. Yearly data were more difficult to interpret due to small number of cases and large year to year fluctuations. Trends could be also analyzed by cause of death. [Figure 2b] Causes other than infectious and

parasitic diseases showed no trend over time, whereas fluctuations in infectious and parasitic diseases explained the large changes documented for all causes combined. Among these infectious and parasitic diseases, most underlying causes were due to HIV/AIDS, to tuberculosis, to diarrhea, to pneumonia and other acute respiratory infections and to meningitis, all conditions closely related with HIV. Therefore, there is no doubt that large fluctuations in under-five mortality in Agincourt were due to HIV/AIDS, and the recent decline started probably around year 2006, and was due most likely due to efforts to control MTCT.

5) Trends in Hlabisa 2000-2009

The Hlabisa DSS (the Africa Center, or ACDIS), is also located in a remote rural area and in a former homeland, is better served because the Hlabisa hospital is well staffed and has been the site of numerous clinical trials and studies focusing on HIV prevention and treatment. As a result, prevention of MTCT started earlier, and its coverage was probably higher than in other rural areas of South Africa. Under-five mortality was rising from 2000 to 2002, reaching a peak of 100 per 1000, then started to decline dramatically, reaching 47 per 1000 in 2009. As was the case in Agincourt, mortality decline was due to a decline in infectious and parasitic mortality, and mostly to HIV/AIDS. [Figure 4] This dramatic decline shows that a reversal of under-five mortality trends can be obtained rapidly, even in a rural and poor community.

6) Relating mortality trends with efforts to reduce MTCT

Few data are available on the up-take of prevention of MTCT in South Africa, and most likely it varied significantly by province. The UNGASS report provides two points in year 2005 (60%) and year 2009 (83%), which allows one to reconstruct the dynamics of the coverage of prevention of MTCT, knowing that it was virtually nil in year 2000. Assuming that the uptake of prevention of MTCT has been regular, and that its efficiency increased over time from 30% in 2001 to 90% in 2010 because of improvements in strategies, one could compute its possible impact on under-five mortality. Results show that the prevention of MTCT from year 2004 to year 2008 could reduce under-five mortality by -17 per 1000. This value is consistent with the value found in Agincourt (-21 per 1000), but lower than the mortality decline found in Hlabisa (-53 per 1000), and higher than that found in vital

registration from the peak in 2006 to 2008 (−6 per 1000). These values appear inconsistent at first glance, and may reveal either data problems, or large variations in coverage and efficacy of the prevention of MTCT, or independent effects of other dynamics. For instance, in Hlabisa, the large scale endeavor of the Africa Center, with numerous physicians and health personnel and a large budget, could well have had a broader impact on general health, beyond HIV/AIDS.

Discussion

HIV/AIDS induced dramatic changes in mortality trends in Africa. In countries most infected by HIV, it induced a doubling- when not a tripling- of under-five mortality, whipping out decades of steady improvements. No national data based on demographic censuses and surveys yet showed any reversal in mortality trends, mainly because last points available predate major uptake in the prevention of mother to child transmission.

However, recent evidence from South Africa, indicates that these negative trends can be reversed as quickly as they rose, so that losses could be compensated in a relatively short time. Data are still preliminary, and will need to be confirmed by more evidence in the coming years.

It is impossible to relate each detailed program for preventing mother to child transmission to mortality trends. However, both at national level and at local level in Agincourt and Hlabisa, it seems that programs aiming at reducing MTCT and possibly at treating infected children had a dramatic effect. By simply analyzing the date at which the reversal in mortality trends occurred, it seems that a large effect was obtained with bi-therapies (AZT+NVP), and probably later with tri-therapies.

These are still the first few years where one could witness resuming the under-five mortality decline in Southern Africa. We do not know the long term effect of the prevention of MTCT, and do not have enough information on treatment of infected children. It remains possible that resistance to ARV's might develop in the future, leading to new changes in trends. However, so far, the first few years of implementation of ARV for prevention and treatment give a rather optimistic perspective, after 15 to 20 years of very pessimistic prospects.

In this paper, we addressed only the case of under-five mortality, simply because more data are available. However, some data also exist for young adults, which could be used for analyzing reversal in mortality trends among adults.

We focused on overall mortality trend. The Hlabisa study has already provided some data on trends by cause of death. A similar analysis is underway in Agincourt. The national vital registration in South Africa could also provide some more information. However, registration of HIV/AIDS as a cause of death at national level was found to be very weak, accounting for only 1 out of 10 deaths expected to be in fact due to AIDS. [Yudkin et al. 2009] The example of Agincourt and Hlabisa based on verbal autopsies indicates that better work could be done when death certificates are filled by physicians.

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Table 1: Estimates of under-five mortality in countries from Southern Africa

Country	HIV Prevalence in 2000 (per 100)	Under five mortality (per 1000)				Change in q(5)	
		Lowest Year	q(5)	Last point Year	q(5)	From Lowest	From expected trends
South Africa	25	1993	47	2006	85	38	65
Zimbabwe	27	1987	61	2005	85	24	55
Namibia	21	1994	63	2006	71	8	37
Botswana	36	1987	47	2006	76	29	57
Lesotho	29	1985	85	2009	126	41	81
Swaziland	36	1991	48	2007	139	91	117

Source: q(5) author's calculation from demographic surveys. HIV prevalence in year 2000 calculated from sentinel sites of ANC clinics.

Figure 1: Under-five mortality trends in sub-Saharan Africa, by level of HIV infection

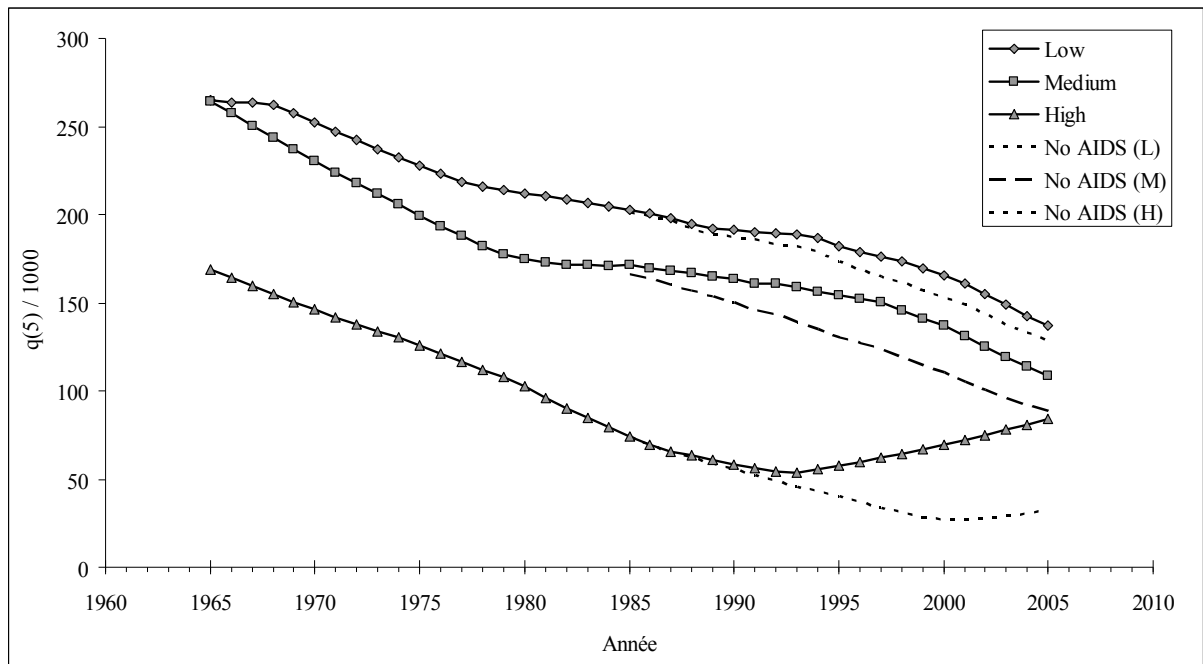


Figure 2: Trends in mortality of children aged 0-9, South Africa, 1997-2008
(vital registration data)

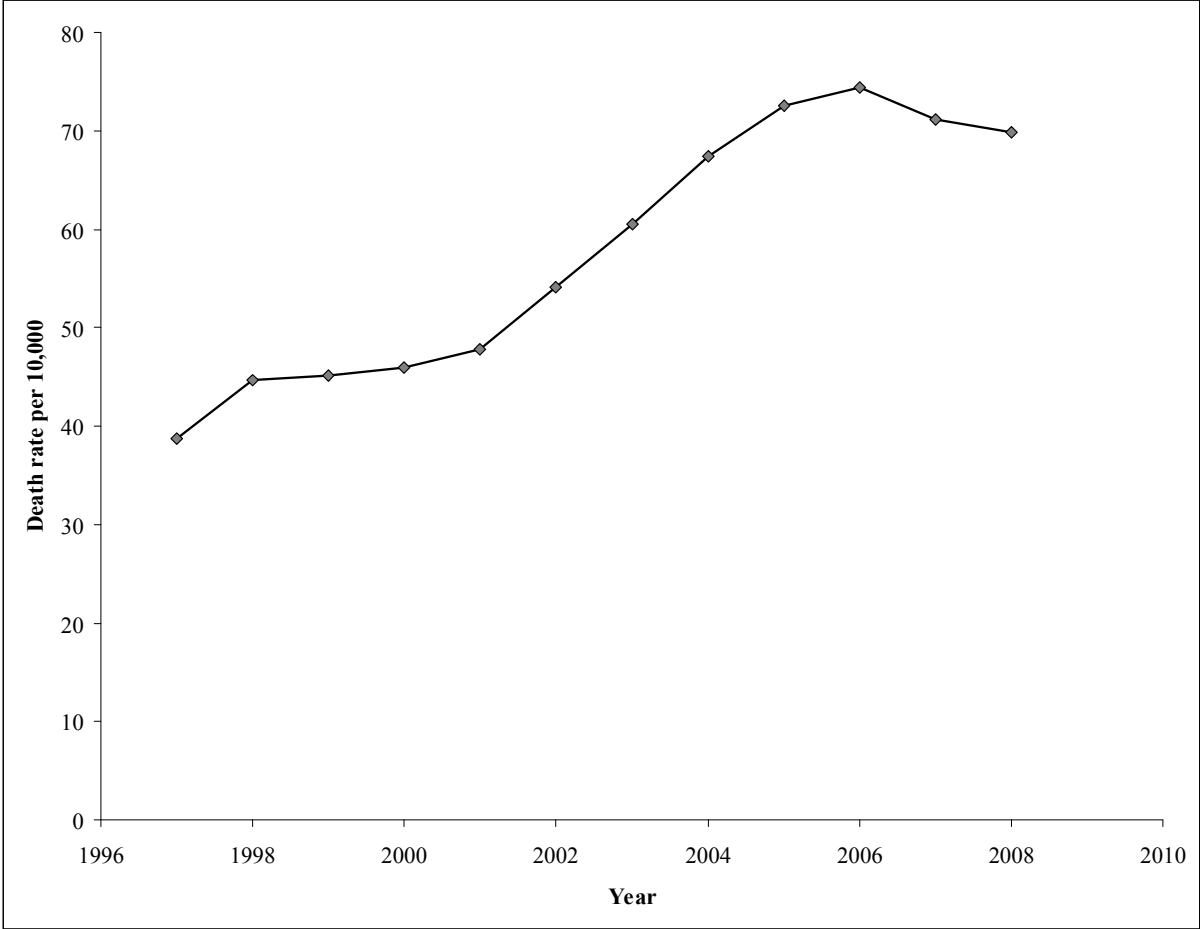


Figure 2: Trends in under-five mortality, Agincourt, South Africa, 1992-2010

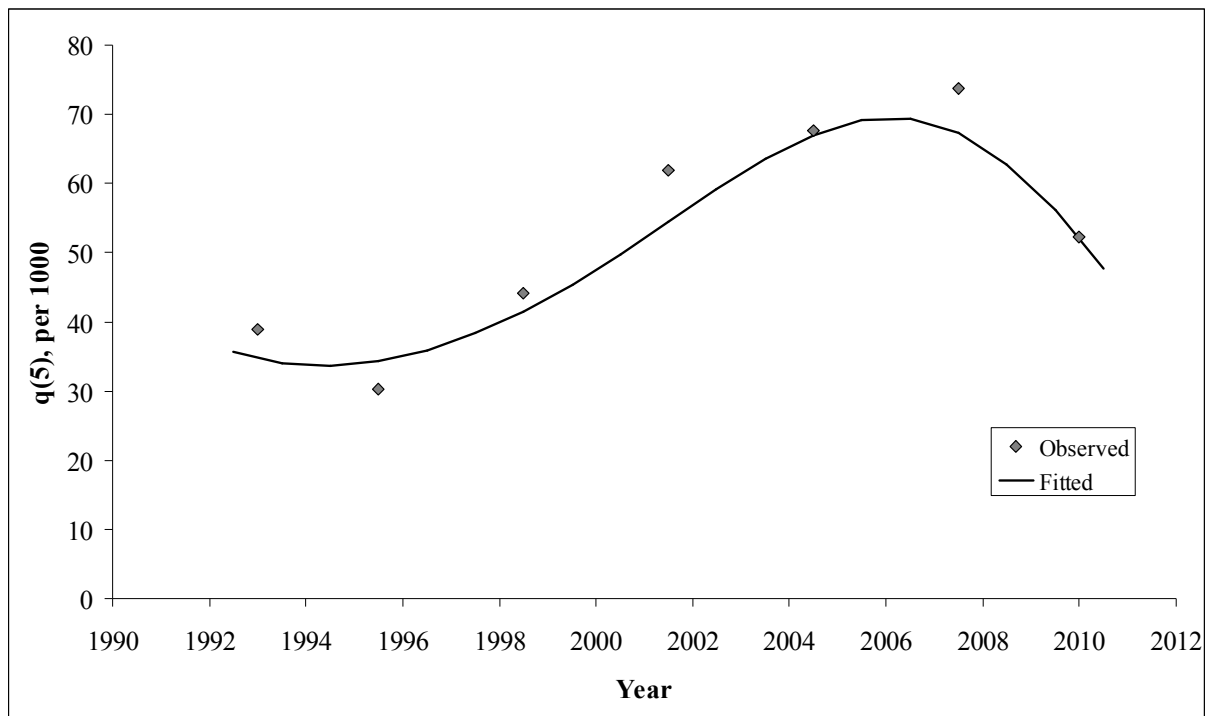


Figure 2b: Trends in under-five mortality by cause, Agincourt, South Africa, 1992-2010

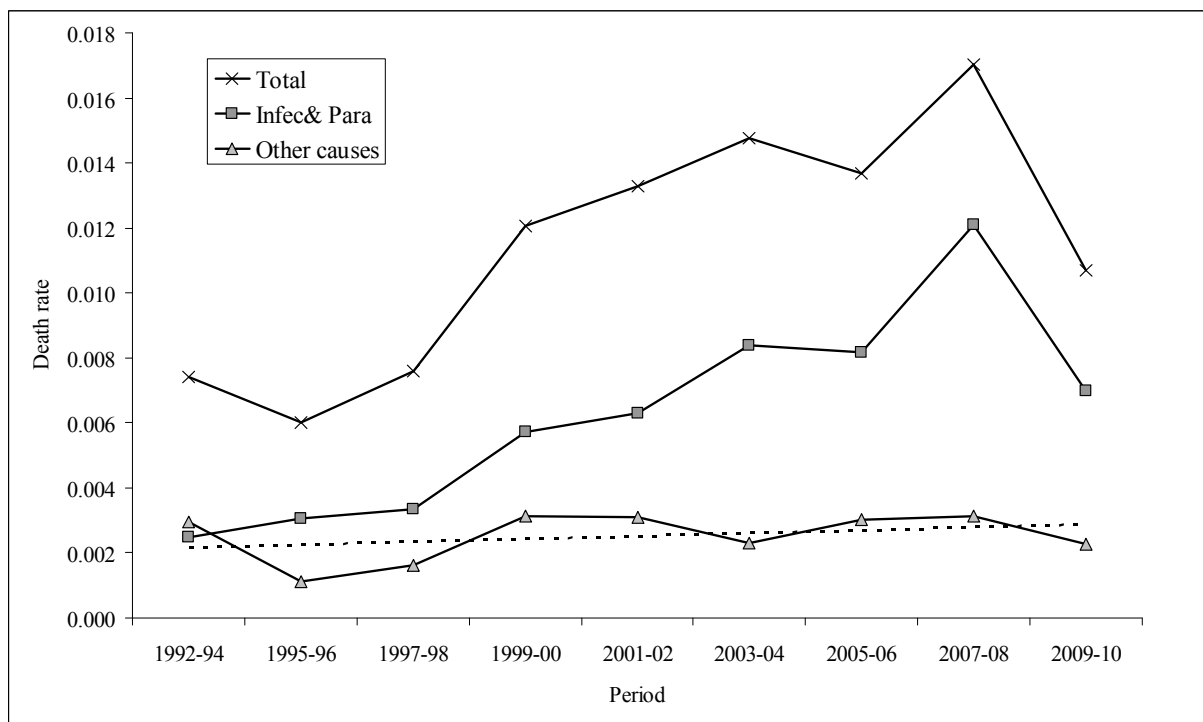
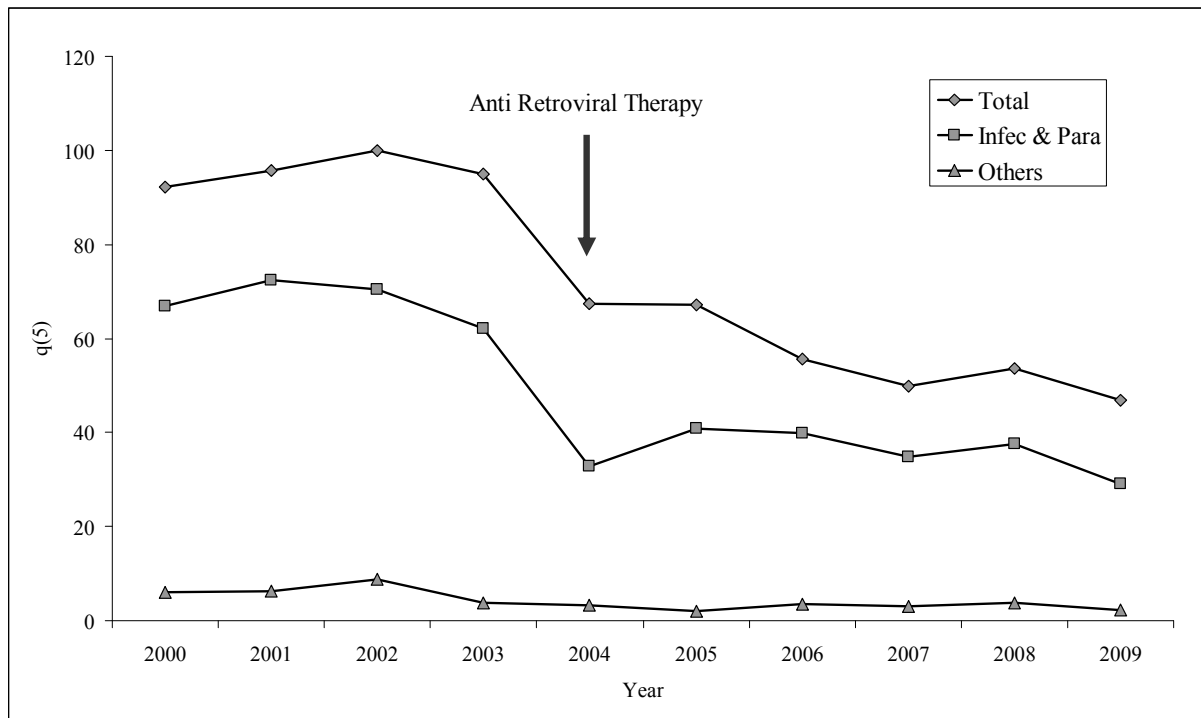


Figure 3: Trends in under-five mortality, Hlabisa, South Africa, 2000-2009



Source: Herbst et al. 2011

Résumé en français

Avec la diffusion des tri-thérapies par anti-rétroviraux, médicaments efficaces contre le sida, la mortalité des jeunes adultes des deux sexes a commencé à baisser, après des années d'augmentation notable dans les pays africains à forte prévalence, et ce depuis environ 2005. Mais ce ne semble pas être le cas pour la mortalité infanto-juvénile, qui a continué à augmenter dans les mêmes pays. Cette étude porte sur les tendances de la mortalité des moins de cinq ans dans six pays d'Afrique australe où la séroprévalence du VIH est supérieure à 20%. Les données sont fournies surtout par les enquêtes EDS, et supplémentées par d'autres données si nécessaire. Les tendances de la mortalité ont été lissées par un modèle linéaire-logistique. Les augmentations de la mortalité sont comparées aux tendances de l'infection chez les femmes enceintes. Les données de deux observatoires de population situés en Afrique du Sud sont aussi analysées : Agincourt et Hlabisa. Les résultats montrent qu'aucune grande enquête nationale n'a encore montré de baisse significative de la mortalité des moins de cinq-ans. Par contre, l'Etat Civil d'Afrique du Sud montre une baisse depuis 2006, l'observatoire d'Agincourt une baisse depuis 2008, et celui de Hlabisa depuis 2004. Ces nouvelles baisses de mortalité sont attribuées à la diffusion rapide de la prévention de la transmission materno-fœtale, et au traitement des enfants infectés avec les anti-rétroviraux.