Transparency and Conservative Values in Chigwedere et al.: The 6.7 Years ARV Treatment Benefit Estimate in "Estimating the Lost Benefits of Antiretroviral Drug Use in South Africa[1]"

Claus Jensen

Chigwedere et al. present a statistical argument that the South African government was responsible for the loss of many lives because of a failure to accept the use of available ARVs to prevent and treat HIV/AIDS in a timely manner.

The Harvard authors are proverbial number crunchers. They do not contribute new data, they do not re-interpret existing data, and they do not carry out any critical analysis of their sources. The purpose in this paper was strictly confined to quantifying alleged lost treatment benefits under the administration of former South African President Thabo Mbeki. Because of the well-known GIGO principle (garbage in, garbage out) attendant on all such calculations and modeling in a study of this nature, a minimum requirement is that the authors provide a scientific rationale for their choice of data going into their calculations, as well as an evaluation of the strengths and weaknesses of the models they rely on both explicitly and implicitly. The main criteria by which Chigwedere et al. choose their sources are what they claim to be their "transparency", "minimization of assumptions" and "conservative[ness]". They refer to these as their "overriding values". In this article, we ask if those values are scientific, and if Chigwedere et al. have adhered to them.

In their introduction Chigwedere et al. write:

We contend that the South African government acted as a major obstacle in the provision of medication to patients with AIDS . . . The intention is to estimate only the lost benefits attributable to the decisions made by the leaders of the South African government. Our overriding values in choosing methods were transparency and minimization of assumptions, and we were purposely conservative.

In the context of apportioning blame, "transparency" becomes politician- or lawyer-speak rather than a recognised scientific value. Minimisation of assumptions, on the other hand, is a scientific value, but here it is linked to the value of being purposely conservative. In science one does not achieve transparency or minimise assumptions by choosing conservative estimates. The basic assumptions on which estimates are made – for instance that HIV causes AIDS – are exactly the same whether the estimate of total cases is high or low. Similarly, in mathematics or epidemiology one does not arrive at the correct result by choosing conservative estimates for one's calculations.

Thus, Chigwedere et al. implicitly admit that their paper is neither scientific nor an honest attempt at arriving at correct figures. It is an inherently biased indictment of named individuals, purporting to quantify the scale of alleged culpability. That is what their stated "values" are about, and that is how their paper has been used by critics of

1 J Acquir Immune Defic Syndr Volume 49, Number 4, December 1, 2008

the Mbeki administration's AIDS policies.[2] Irrespective of whatever merit their calculations may have in the political or legal arena, this scientifically pointless quantification of guilt does not belong in a medical journal.[3]

With regard to transparency and minimisation of assumptions, a glance at the paper's references reveals such rhetoric as empty even on its own terms. Consider as example the touted conservative estimate of the lost benefits of ARVs:

we used the very conservative estimate of an average ARV treatment benefit of 6.7 years per patient. Bachmann[21] determined that ARV for disease treatment would prolong life by 6.7 years if provided late in disease development and by 9.8 years if provided earlier. This estimate is also lower than the low end of average benefits (7.8–13.3 years) that have been modeled for ARV treatment in the United States.[22]

The 330,000 "lives lost" under President Mbeki each represent a 6.7-year shortening of life-span, according to Chigwedere. How transparent is the Bachmann et al reference? Bachmann et al. write:

None of the latter three South African studies compared ARV with antibiotics or early with late treatment. The present study was intended to fill these gaps. (…)Randomized trials in African adults have shown antibiotics to be effective, cotrimoxazole reducing morbidity or death by 30% regardless of stage of HIV/AIDS (Grimwade & Swingler, 2003), and isoniazid reducing tuberculosis incidence by 35% (Woldehanna & Volmink, 2004). ARV has however not been compared with cotrimoxazole or isoniazid in randomized trials. The higher background risk of infectious diseases such as tuberculosis in Southern Africa, and cost differences, impair the generalizability of HIV/AIDS drug trials conducted in developed countries. A key question is the optimal time to start treatment, especially considering the long duration of treatment if effective, and the high probability of developing ARV resistance (Phillips et al., 2003). Quantitative models can help synthesize and apply incomplete evidence. In the US, for example, Freedberg et al. (2001) estimated that triple ARV started at a late stage of HIV/AIDS (CD4_ 87 cells/ml) could prolong life by about 1.3 discounted QALYs.

The respective benefits of ARV and antibiotics arrived at are not the direct result of clinical trials in Africa. Bachmann et al. substitute models, partly based on observations in Europe and the US, for clinical trials in order to make up for the insufficient data. Perhaps this is why Chigwedere et al. feel they have to make the case that observations in the US and Europe are relevant to South Africa:

Primary studies done in Africa (including South Africa), a meta-analysis, and a comparison with the developed countries show that other than increased mortality at the start of treatment, patientresponses to ARV treatment in Africa are similar to those observed in the developed world.[20]

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2 http://aidstruth.org/features/2009/south-africa-needs-hivaids-truth-commission
http://news.harvard.edu/gazette/story/2009/10/hiv-denial-conspiracy/

3 *JAIDS Journal of Acquired Immune Deficiency Syndromes, non-HIV, and AIDS-related information from all relevant clinical and basic sciences, with a strong focus on molecular biology, cell biology, epidemiology, and clinical virology. Each issue of JAIDS publishes vital information on the advances in diagnosis and treatment of HIV and non-HIV infectious [sic], as well as the latest research in the development of therapeutics and vaccine approaches.*

The reference here is Bratstein et al.[4], who write:

Mortality rates of HIV-infected patients from low-income settings in Africa, South America, and Asia fell substantially within the first few months of HAART, and approached those seen in Western Europe and North America after 4–6 months. Patients in low-income settings started treatment with considerably more advanced immunodeficiency than those from industrialised countries, but virological and immunological response to HAART were similar in both settings

By mortality rates in low-income settings "approaching those seen in high-income settings" is meant that mortality rates per 1000 person-years during the first 6 months of treatment were 353 to 24, whereas in the last 6 months it fell to 27[5] to 16. In other words, the mortality rate in low-income settings fell from almost 15 times higher than high-income settings in months 1-6 to about 35% higher in months 6-12. Although one can use the word "approaching" in the sense that the differences become less over time, there is nothing in this to suggest any similarity between mortality in low-income and high-income settings. Chigwedere et al. consequently have no basis for making this claim, and their conflation of "patient responses" in terms of molecular markers with clinical endpoints is highly misleading.

In order to impress the reader with the conservativeness of their chosen 6.7 year treatment benefit estimate, Chigwedere et al. compare it with Walensky et al., who, as we saw above, estimate 7.8-13.8 saved life-years for American HIV positives, where Bachman et al. have 6.7-9.8 life-years for low-income settings.

However, the same ART Cohort Collaboration, which provided the 6.7-9.8 life-years estimate for low-income settings tells us in another paper[6] **,** that survival benefit[7] for HIV positives infected at age 20 in Europe and the US increased from 26 life-years to 39 life-years between 1996-2005. This is corroborated by Lohse et al.[8], who estimate that a 25 year old newly diagnosed HIV positive between 2000-2005 in Denmark could expect an average 22.5 years of survival benefit[9] . Where Walensky et al. estimated that the survival benefit increased from 8.2 life-years in 1996 to 13.3 life-years by 2003, Lohse et al. saw an increase from 12.5 life-years in the period 1997-1999 to 22.5 in the period 2000-2005. Notably, the Danish study included all patients, regardless of "such prognostic factors as CD4-positive cell count, HIV RNA, disease stage, history of AIDS treatment adherence, or time receiving HAART". Individuals with no known hepatitis C infection had 29 years of estimated survival benefit.

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4 *ART Cohort Collaboration (ART-CC). Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries.* Lancet. *2006;367:817–824*

5 It would be justified to look into this abrupt drop in low-income mortality at the 4-6 months mark, but that is not our current errand.

6 Antiretroviral Therapy Cohort Collaboration. *Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies.*

7 Survival benefit is arrived at by subtracting estimated average time from untreated HIV infection to death (10 yrs.) from the estimated life expectancy on HAART. Since this study deals with general life expectancy and since it is well known that HIV positives are in high-risk groups for life-style diseases, suicides etc., the estimated survival benefit of ARVs is likely understated.

8 *Survival of Persons with and without HIV Infection in Denmark, 1995–2005*
http://www.annals.org/content/146/2/87.full.pdf

9 See footnote 7

Why did Chigwedere et al not report the life-expectancy estimates for high-income settings from the same cohort collaboration they used to argue that patient response to ARV is similar in high and low-income settings? One can only assume that in this case they were being "purposely conservative" to make the reader accept that survival benefits of HAART in South Africa are similar to the US and Europe.

In another paper from the ART Cohort Collaboration, which, as we saw above, reported 13 years increase in life-expectancy between 1996-2005, the researchers struggled to find statistically significant increase in survival rates when examining first and second-year mortality in the US and European cohorts. As can be seen in the tables below, the only possibly significant drop in mortality between 1997-2003 is in the last year of observation, prompting the authors to conclude:

INTERPRETATION: Virological response after starting HAART improved over calendar years, but such improvement has not translated into a decrease in mortality.

First-Year Mortality

1995/96: total n=1232 / #deaths=27 (2.2%)
1997: 4785 / 98 (2.1%)
1998: 4583 / 85 (1.9%)
1999: 3699 / 67 (1.8%)
2000: 3203 / 63 (2.0%)
2001: 2783 / 49 (1.8%)
2002/3: 1932 / 25 (1.3%)

Second-Year Mortality (cumulative)

1995/96: 1232 / 53 (4.3%)
1997: 4785 / 151 (3.2%)
1998: 4583 / 144 (3.1%)
1999: 3699 / 109 (3.0%)
2000: 3203 / 99 (3.1%)
2001: 2783 / 69 (2.5%)

A commentary in *The Lancet* suggests that the surprising outcome was due in large part to increased tuberculosis incidence, stemming from migration from Third World countries, including African countries, and a change in study population characteristics towards more females and more heterosexuals.

Importantly, the recent increase in AIDS risk seemed largely because of increased tuberculosis incidence. Another major feature of the study, and the probable explanation for these somewhat paradoxical trends, was the changing characteristics of the study population: from 1995–96 to 2002–03, large increases in female (16% to 32%) and heterosexual (20% to 47%) proportions were balanced by a declining male homosexual proportion (56% to 34%). A major shift in antiretroviral class was also seen, with use of non-nucleoside reverse-transcriptase inhibitors increasing from 2% to 40% and regimens based on protease inhibitors declining from 95% to 45%. Although data on country of birth were not available, given migration patterns to the countries involved, the increased incidence of tuberculosis probably reflected higher proportions of study participants born in regions with a high prevalence of

tuberculosis. We have shown large contrasts in the spectrum of opportunistic disease by country of birth in the Australian HIV-infected population, especially the higher risk of tuberculosis in individuals born in Africa and Asia.[10]

As can be seen, a trend towards just three of the characteristics of South Africa's HIV positive population is thought to have offset almost all the expected positive results of improved HAART therapy in Europe and North America in the first and second years of observation. If this is indeed the case, one would expect the same circumstances to continue to exert a strong influence on the results of treatment in South Africa beyond the established higher mortality in the first year of HAART. Thus, in order to explain poor results, these researchers do not hesitate to contradict the conclusion that patient responses to ARV treatment in Africa are similar to those observed in the developed world.

Comparisons not only between South Africa and industrialised nations, but also between various demographics and time periods are far from "transparent"[11]. The authors of *Life expectancy of individuals on combination antiretroviral therapy in high-income countries* introduce their study thus:

Combination antiretroviral therapy has led to significant increases in survival and quality of life, but at a population-level the effect on life expectancy is not well understood.

How, then, could it be well understood in low-income settings?

Moreover, the calculations of survival benefit/life expectancy are all projections into the unknown, replete with untested assumptions. Most studies estimate life expectancies for HIV positives far greater than the duration of the entire HIV/AIDS era, including the HAART era. Lohse et al. recognise this in their disclaimer: "survival predictions were based on the assumption that the observed mortality rates also would apply in subsequent years".

Chigwedere et al. mention none of these uncertainties. Instead they cherry-pick references in an attempt to persuade the reader that the figures going into their calculations carry with them a degree of certainty; and deceptively pretend that their arbitrarily applied "conservativeness" criteria is meaningful, even on its own terms.

Conclusion:

Chigwedere et al. use (gu)e(s)stimates, based on unexamined data, based in turn on unexamined assumption, as well as misleading language to arrive at conclusions, which are presented as statistical factoids, whose only margin of error is on the side of caution. A closer examination of the Harvard authors' appeal to values of transparency, minimisation of assumptions and conservativeness reveals them as an extension of their preconceived notions of the culpability of named individuals.

10 http://ummafrapp.de/skandal/haart/annex%202.pdf

11 This includes aspects, such as different/changing therapy recommendations, different/changing drugs, different/changing definitions of AIDS, different/changing tests, and different/changing test criteria/interpretations.

The authors' choice of references reflects the same bias as their alleged values. Both are selected to establish an appearance of scientific objectivity where none exists. This is the opposite of transparency.

Harvard and Journal of Acquired Immune Deficiency Syndromes are held in high esteem, it is therefore deeply disappointing to find that they so easily abandon the scientific search for truth to publish political witch hunts dressed up as statistical science.