CONCISE COMMUNICATION

Dramatic increase in HIV prevalence after scale-up of antiretroviral treatment

Jaffer Zaidi[a], Erofili Grapsa[a], Frank Tanser[a],
Marie-Louise Newell[a,b] and Till Bärnighausen[a,c]

Objectives: To investigate HIV prevalence trends in a rural South African community after the scale-up of antiretroviral treatment (ART) in 2004.

Methods: We estimated adult HIV prevalence (ages 15–49 years) using data from a large, longitudinal, population-based HIV surveillance in rural KwaZulu-Natal, South Africa, over the period from 2004 (the year when the public-sector ART scale-up started) to 2011. We control for selection effects due to surveillance nonparticipation using multiple imputation. We further linked the surveillance data to patient records from the local HIV treatment program to estimate ART coverage.

Results: ART coverage of all HIV-infected people in this community increased from 0% in 2004 to 31% in 2011. Over the same observation period adult HIV prevalence increased steadily from 21 to 29%. The change in overall HIV prevalence is nearly completely explained by an increase of HIV-infected people receiving ART, and it is largely driven by increases in HIV prevalence in women and men older than 24 years.

Conclusion: The observed dramatic increase in adult HIV prevalence can most likely be explained by increased survival of HIV-infected people due to ART. Future studies should decompose HIV prevalence trends into HIV incidence and HIV-specific mortality changes to further improve the causal attribution of prevalence increases to treatment success rather than prevention failure.

© 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

Introduction

Changes in HIV prevalence over time have in the past commonly been used to assess the success of national HIV responses, with increasing HIV prevalence taken to indicate failure of HIV prevention strategies [1–3].

However, such use of HIV prevalence data may become increasingly misleading, as large-scale antiretroviral treatment (ART) intervenes in the course of the HIV epidemic. Effective ART substantially increases survival of HIV-infected populations [4−7] and can decrease HIV transmission probabilities [8,9]. Mathematical models

have predicted that the net impact of these two counter-acting ART effects will be an increase in HIV prevalence, at least over the coming decades [10]. However, this impact has not been empirically documented.

We examine for the first time HIV prevalence trends following the start of ART scale-up in one of the HIV hyperendemic communities in sub-Saharan Africa, using data from the longitudinal, population-based HIV surveillance conducted by the Africa Centre for Health and Population Studies (Africa Centre) in rural Kwa-Zulu-Natal, South Africa [11]. KwaZulu-Natal is the province with the currently highest prevalence of HIV in South Africa and, as a consequence, with the highest adult mortality [12,13]. In this study, we quantify HIV prevalence and ART coverage trends over the period 2004−2011 and examine trend differentials by sex and age group to inform hypotheses about the relationship between HIV prevalence and the local ART scale-up.

Methods

Setting
The Africa Centre setting and the HIV surveillance are described in the Appendix and elsewhere [11,14]. The Hlabisa HIV Treatment and Care Programme had 16 000 individuals actively on ART at the end of 2011, of which about 40% or 6500 resided in the Africa Centre demographic surveillance area [15].

Data for HIV prevalence estimation
To ensure comparability of the HIV data over time, we restricted our annual samples to men and women aged 15−49 years, even though since 2007 all adults 15 years or older were eligible for HIV testing in the surveillance. Sample sizes (and participation rates) in the years 2004−2011 were, respectively: 19 907 (57.6%); 27 303 (31.5%); 21 121 (37.7%); 20 211 (32.3%); 21 180 (30.6%); 18 339 (29.7%); 19 254 (37.7%); 17 618 (36.9%). Participation rates by calendar year, sex, and age group are reported in the appendix. The denominator of the participation rates is based on near-complete population enumeration (response rate greater than 99%) through the Africa Centre surveillance system. The denominator includes all individuals eligible for HIV testing, that is, both those who the surveillance fieldworkers successfully contacted for HIV testing consent and those who could not be contacted. Consent rates, that is, the percentages of successfully contacted individuals who agreed to provide blood for an HIV test, were significantly higher (e.g. 51% in 2010 and 63% in 2011).

Data for antiretroviral treatment coverage estimation
To estimate ART coverage of the HIV-infected people included in the samples described above, we matched the individuals who were eligible to participate in the population-based HIV surveillance to the patients in the local HIV treatment program, using data on first name, last name, sex, birth date, and South African identification number [16].

Statistical analysis
We computed crude HIV prevalence estimates for the entire eligible population, and sex and age subgroups, for each year from 2004 to 2011. To control HIV prevalence estimates for selective surveillance participation, we accounted for selection on a wide range of observed variables (age, sex, urban vs. rural residence, household wealth, employment status, and educational attainment) using multiple imputation with chained equations (see Appendix for further details, http://links.lww.com/QAD/A359). Five complete data sets for HIV status were constructed from the imputation procedure using the R package MICE [17]. To obtain prevalence estimates and 95% confidence intervals from the five completed imputed datasets, we used the standard multiple imputation approaches [18,19]. All statistical analyses were performed in R version 2.14.2.

Results

We found a steady and substantial increase in both crude and imputed HIV prevalence for the adult population in this community over the observation period 2004−2011. (Fig. 1 and Appendix Table S5, http://links.lww.com/QAD/A359). This change in overall HIV prevalence is nearly completely explained by an increase of HIV-infected people receiving ART (Fig. 1). When we stratify the prevalence estimates by sex and broad age groups, we find that the increases in overall HIV prevalence are largely driven by the prevalence trends in women and men aged 25−49 years (Fig. 2 and Appendix Tables S3 and S4, http://links.lww.com/QAD/A359). We do not find a similar trend in women and men aged 15−24 years. Although there appears to be an increase over time in HIV prevalence in the youngest age group (15−19 years) in both men and women (which might be interpreted to indicate increasing HIV incidence), these increases do not reach statistical significance.

ART coverage increased rapidly over time, reaching levels greater than 30% of all HIV-infected adults in 2011 (Fig. 1). In all years, ART coverage was higher in women aged 25−49 years compared with men in the same age group, and it was higher in both women and men aged 25−49 years than in younger age groups (Appendix Table S6, http://links.lww.com/QAD/A359).

To test the robustness of our findings, we conducted additional analyses using methods similar to those introduced by Floyd et al. [20]. We added HIV status
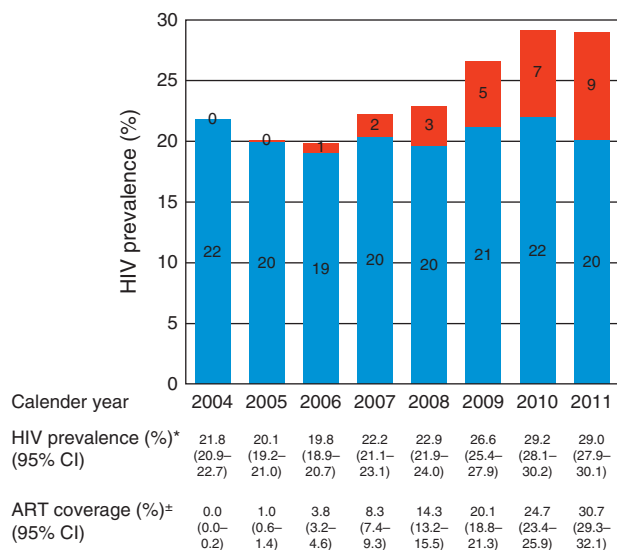
Fig. 1. HIV prevalence and ART coverage trends, 2004–2011. ART, antiretroviral treatment; CI, confidence interval. The figure is based on the analysis of complete cases. *HIV prevalence is expressed in percent of all adults aged 15–49 years. +ART coverage is expressed in percent of all HIV-infected adults aged 15–49 years. The total bars in the figure represent overall HIV prevalence. The red components of the bars represent the HIV-infected people who are receiving ART (in percent of the entire population aged 15–49 years); the blue components of the bars represent the HIV-infected people who are not receiving ART (in percent of the entire population aged 15–49 years).

data available at one point in time from the same individual who at another point in time refused an HIV test to proxy HIV status at the date of refusal. For this purpose, we used data closest in time to the date when an individual refused to participate in the HIV surveillance within specified time windows (of 1, 2, and 3 years)
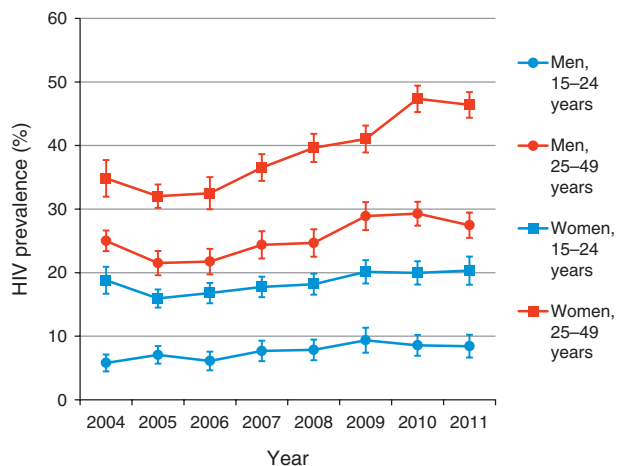
Fig. 2. HIV prevalence estimates by sex and age group. The estimates in this figure are imputation-adjusted. The error bars indicate the 95% confidence intervals.

around this date. All annual HIV prevalence estimates (both those based on complete cases and after multiple imputation) remained essentially unchanged in these three additional analyses (Appendix Figures S1 and S2, http://links.lww.com/QAD/A359).

Discussion

We found a dramatic increase in overall adult HIV prevalence in a community in rural KwaZulu-Natal over the past 8 years, following the public sector scale-up of ART in South Africa. It is likely that this increase is a causal effect of the ART scale-up. ART was scaled up quickly over the observation period, reaching almost 40% (30%) of all HIV-infected women (men) aged 25–49 years. As a result, HIV-related mortality in this community has markedly declined [4,7,21]. At the same time, HIV incidence has remained high over the past years [22], but has not increased and has recently started to decline [23], so that it is unlikely that the HIV prevalences trend could have been caused by increasing incidence. When we divide HIV prevalence into the group of HIV-infected people receiving ART and the group not receiving ART, the prevalence increase over time is almost completely explained by the growth of the former group. Our result that HIV prevalence increases in older women and men is largely responsible for the increase in overall adult prevalence lends further support to the interpretation that the ART scale-up is the cause of the observed trends.

Our findings confirm for the first time empirically the results of recent mathematical modeling studies, which predict that the net effects of ART will lead to HIV prevalence increases over the coming years despite the transmission-reducing effects of treatment [10,24]. Although HIV prevalence has overall dramatically increased since 2004 in older women in this community, our data seem to indicate that prevalence is stabilizing in 2011, despite continuing increases in ART coverage. Plausible explanations of this most recent trend include changing composition of people initiating ART and changing ART adherence over time. Further empirical and modeling studies are needed to continue tracking and explaining HIV prevalence trends in this community.

Our study has several limitations. For one, it is descriptive in nature and our interpretation that the observed HIV prevalence increases are due to ART is based on our understanding of HIV epidemic dynamics and background information on the community in which the study took place. Future studies in this and other population-based cohorts are needed to confirm that observed prevalence increases are causally attributable to the survival benefits of ART. Such studies could also contribute to decomposing the different effects of ART that can contribute to the net changes in HIV prevalence:

the direct effect on survival in HIV-infected people receiving ART, the transmission-reducing ART effects, behavioral effects of ART, and any survival spillover effects in people not receiving ART. It is for instance possible that ART affects the delivery of other life-saving health services [25,26]. In as far as these services differentially benefit HIV-infected and HIV-uninfected populations, ART spillover effects could lead to changes in HIV prevalence.

We have accounted for selection on a wide range of observed variables in multiple imputation and have further demonstrated the robustness of our results to widening the window of time within which HIV status data on an individual is used for the analyses. Despite these results indicating robustness, we cannot completely rule out that endogenous selection has affected our findings. In particular, it is plausible that people who know of their positive HIV status are less likely to participate in HIV surveillance than other population sub-groups [16]. However, we can predict the direction of the potential bias due to this case of endogenous selection. As HIV status knowledge has increased in this community over time following the local ART scale-up and intensified public HIV testing campaigns, we would expect to have underestimated the steepness of the HIV prevalence time trend. The only principled approach to control for endogenous selection is Heckman-type selection models, which have been applied to HIV prevalence estimation by Bärnighausen and coworkers [27,28] using the identity of the HIV fieldworker as a selection variable. Future studies in this community should replicate this approach to confirm the findings published in the present article.

Our findings have a number of important implications for health policy and research. First, the common causal attribution of HIV prevalence trends to a failure of HIV prevention becomes untenable in geographical areas where ART scale-up has reached high levels. It is likely that in other communities in Southern Africa that have benefited from the recent scale-up of ART HIV prevalence increases will soon be observed, which will be due to improved survival of HIV-infected people, rather than due to HIV incidence increases. As mathematical models have shown, in the initial years following ART scale-up [10,24] the survival benefits outweigh the incidence reductions due to ART, leading to HIV prevalence increases, whereas in the longer run the ART-induced reductions in HIV incidence may decrease prevalence.

Second, methods to estimate HIV incidence based on HIV prevalence changes observed in independent cross-sectional samples of the same populations over time, become increasingly difficult to use in the dynamic stages of ART scale-up, when the survival of HIV-infected populations is constantly improving, leading to increasing HIV prevalence.

Third, as individuals, households and communities make decisions based on expectations about their health and survival, it will be important to ensure that people in areas with increasing HIV prevalence due to successful HIV treatment programs understand that these increases are not the result of increases in the force of the epidemic, but rather reflect the good news that HIV treatment is improving the life expectancies of people who have been infected in the past. As HIV prevalence increases will likely soon be observed in other parts of Southern Africa, it will be crucial that governments and community organizations design effective messages to communicate the reason for these increases.

Acknowledgements

Conflicts of interest
All authors declare that they have no conflicts of interest.

References

1. Okware S, Opio A, Musinguzi J, Waibale P. **Fighting HIV/AIDS: is success possible?** *Bull World Health Organ* 2001; **79**:1113–1120.
2. Goldberg AB, Fox AM, Gore RJ, Bärnighausen T. **Indicators of political commitment to respond to HIV.** *Sex Transm Infect* 2012; **88**:e1.
3. Chopra M, Lawn JE, Sanders D, Barron P, Abdool Karim SS, Bradshaw D, et al. **Achieving the health millennium development goals for South Africa: challenges and priorities.** *Lancet* 2009; **374**:1023–1031.
4. Herbst AJ, Cooke GS, Bärnighausen T, KanyKany A, Tanser F, Newell ML. **Adult mortality and antiretroviral treatment rollout in rural KwaZulu-Natal, South Africa.** *Bull World Health Organ* 2009; **87**:754–762.
5. Mills EJ, Bakanda C, Birungi J, Chan K, Ford N, Cooper CL, et al. **Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda.** *Ann Intern Med* 2011; **155**:209–216.
6. Boulle A, Van Cutsem G, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. **Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa.** *AIDS* 2010; **24**:563–572.
7. Bor J, Herbst AJ, Newell ML, Bärnighausen T. **Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment.** *Science* 2013; **339**:961–965.
8. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med* 2011; **365**:493–505.
9. Attia S, Egger M, Muller M, Zwahlen M, Low N. **Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis.** *AIDS* 2009; **23**:1397–1404.
10. Hontelez J, de Vlas S, Baltussen R, Newell M-L, Bakker R, Tanser F, et al. **The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa.** *AIDS* 2012; **26**:S19–S30.

11. Tanser F, Hosegood V, Bärnighausen T, Herbst K, Nyirenda M, Muhwava W, *et al.* **Cohort Profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey.** *Int Epidemiol* 2008; **37**:956–962.
12. Department of Health. *Global, AIDS., response progress report: Republic of South, Africa.* Pretoria, Republic of South Africa: Department of Health; 2012.
13. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. **The health and health system of South Africa: historical roots of current public health challenges.** *Lancet* 2009; **374**:817–834.
14. Bärnighausen T, Hosegood V, Timaeus IM, Newell ML. **The socioeconomic determinants of HIV incidence: evidence from a longitudinal, population-based study in rural South Africa.** *AIDS* 2007; **21 (Suppl 7)**:S29–38.
15. Houlihan CF, Bland RM, Mutevedzi PC, Lessells RJ, Ndirangu J, Thulare H, *et al.* **Cohort profile: Hlabisa HIV treatment and care programme.** *Int J Epidemiol* 2011; **40**:318–326.
16. Bor J, Bärnighausen T, Newell C, Tanser F, Newell ML. **Social exposure to an antiretroviral treatment programme in rural KwaZulu-Natal.** *Trop Med Int Health* 2011; **16**:988–994.
17. van Buuren S, Groothuis-Oudshoorn K. **MICE: Multivariate imputation by chained equations in R.** *J Stat Software* 2011; **45**:1–67.
18. Hontelez JAC, de Vlas SJ, Tanser F, Bakker R, Bärnighausen T, Newell ML, *et al.* **The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa.** *PloS One* 2011; **6**:e21919.
19. Rubin DB. *Multiple imputation for nonresponse in surveys.* New York: Wiley Online Library; 1987.
20. Floyd S, Molesworth A, Dube A, Crampin AC, Houben R, Chihana M, *et al.* **Underestimation of HIV prevalence in surveys when some people already know their status, and ways to reduce the bias.** *AIDS* 2013; **27**:233–242.
21. Mutevedzi PC, Lessells RJ, Heller T, Bärnighausen T, Cooke GS, Newell ML. **Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes?** *Bull World Health Organ* 2010; **88**:593–600.
22. Bärnighausen T, Tanser F, Newell ML. **Lack of a decline in HIV incidence in a rural community with high HIV prevalence in South Africa.** *AIDS Res Human Retroviruses* 2009; **25**:405–409.
23. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. **High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa.** *Science* 2013; **339**:966–971.
24. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, *et al.* **HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa.** *PLoS Med* 2012; **9**:e1001245.
25. Grepin KA. **HIV donor funding has both boosted and curbed the delivery of different non-HIV health services in sub-Saharan Africa.** *Health Aff (Millwood)* 2012; **31**:1406–1414.
26. Mills EJ, Bärnighausen T, Negin J. **HIV and aging: preparing for the challenges ahead.** *N Engl J Med* 2012; **366**:1270–1273.
27. Bärnighausen T, Bor J, Wandira-Kazibwe S, Canning D. **Correcting HIV prevalence estimates for survey nonparticipation using Heckman-type selection models.** *Epidemiology* 2011; **22**:27–35.
28. Hogan DR, Salomon JA, Canning D, Hammitt JK, Zaslavsky AM, Bärnighausen T. **National HIV prevalence estimates for sub-Saharan Africa: controlling selection bias with Heckman-type selection models.** *Sex Transm Infect* 2012; **88 (Suppl 2)**:i17–i23.