Overview of Masters Research (Analytics Application to the Insurability of Chronic Conditions)

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Background: The scale-up of combination antiretroviral therapy (ART), one of the greatest pharmacological interventions in human history, has reduced adult HIV-related deaths in South Africa by around 70% between the peak in 2005 and 2019, but it is unclear from published studies in South Africa and globally which subgroups of HIV-infected adults, defined by both baseline and current (time-updated) characteristics, may achieve HIV-uninfected levels of mortality and which subgroups have relative mortality that is within the insurance industry's threshold for insurability. Relative mortality estimates are important in insurance since insurability is measured by relative mortality, not absolute mortality or other measures such as life expectancy. As HIV-infected people survive to increasingly longer durations of ART, there is a need for patients, healthcare practitioners, ART programmes, other modellers, insurers and policymakers to understand the prognosis when measured from later durations on ART based on current characteristics. However, most South African studies are based on baseline characteristics, short follow-up times, and low patient volumes, and they lack an HIV- uninfected control selected from the same subpopulation for estimating relative mortality. At the time of initiating this research in 2013/2014, some insurers were declining HIV-infected South Africans applying for higher cover amounts spanning the whole of life. Further, other chronic conditions such as Type 2 Diabetes (DM2) had already been insurable for many years in South Africa. At the same time, the ART Cohort Collaboration (ART-CC) assessed the insurability of HIV-infected people starting ART in Europe and issued an urgent call for a corresponding study in South Africa. This study responds to this call and, to the author's knowledge, is the first study outside of Europe to assess the insurability of HIV-infected adults starting ART by assessing the relative mortality of South African HIV-infected adults initiating ART using an HIV-uninfected control (comparator) chosen from the same subpopulation, measured from multiple time points on ART using both baseline and current characteristics, long follow-up times, significant patient volumes and accurate mortality ascertainment. The study identifies patient subgroups with insurable levels of relative risk as well as subgroups that attain HIV-uninfected levels of all-cause mortality and is fundamental for evaluating ART programmes and for informing evidence-based insurance decisions that are actuarially sound and treat insurance customers fairly.

Methods: A retrospective cohort study is performed using patient data from a large medical scheme population and Aid for AIDS (AfA), a private sector HIV managed care programme in South Africa. Three cohorts are extracted from the same medical scheme population: HIV-infected adults starting ART, patients with DM2

starting hypoglycaemic therapy, and an HIV- uninfected and DM2-negative control (comparator). Mortality is ascertained via linkage with the national death registry. Relative all-cause mortality risk (relative risk) is estimated using a generalized linear model (GLM)assuming a Poisson error distribution and with expected numbers of deaths based on the control cohort mortality according to age, gender and population group specified as an offset. To meet insurers' needs for estimates of future relative risk that remain constant across the policy lifetime and incorporate current characteristics nearest to the time of applying for insurance, relative risk is estimated from each 6-month time point on ART over the remaining follow-up according to the patient's length of time on ART at the time of applying for insurance, current CD4 count and viral load and baseline CD4 count.

Results: In the HIV cohort, 8,920 deaths were observed recorded in 77,325 patients starting ART between 2000 and 2013 followed for 315,341 person years of observation (PYO) (median follow-up of 3.23 years [IQR 2.04; 5.30]). In the DM2 cohort, 7,970 deaths were recorded in 67,705 patients starting antihyperglycaemic therapy between 2000 and 2013 followed for 365,547 PYO (median follow-up of 6.20 years [IQR 3.85; 9.53]). In the control, 24838 deaths were recorded in 512,940 patients followed for 3,276,501 PYO. The median CD4 count in the overall HIV cohort reached the lower limit of CD4 count in HIV uninfected people (500 cells/μl) after 5 years on ART and, after 12 months on ART, 77% of patients were virologically suppressed (viral load $\leq$ 400 copies/ml), increasing to 80% after 10 years on ART. Within the first 6 months on ART, 21% of patients attained both a CD4 count above 200 cells/μl and a suppressed viral load, increasing to 49% in months 6-12, 68% in years 1-2 and 80% after 10 years on ART. In the overall HIV cohort, 90% of patients at risk from all time points 6 months or later since ART initiation were estimated to have relative risk within the insurance industry threshold (< 5). Within patients attaining current CD4 counts of 200+ cells/μl and suppressed viral loads ($\leq$ 400 copies/ml) at 6 months on ART or later, 100% of patients at risk corresponded to relative risk levels well below the insurance industry threshold (< 5). 90% of patients at risk from 1 year of ART onwards had a lower or comparable relative risk to the DM2 cohort, implying that the majority of patients on ART had comparable relative risk to those with a chronic condition that is already insurable. Baseline CD4 count was only prognostic for relative risk within the first three years of ART after adjusting for the immunological and virological response to ART. Patients attaining a current CD4 count of 200+ cells/μl and a suppressed viral load ($\leq$ 400 copies/ml) had the lowest relative risk, reducing with time on ART and approaching 1 after 3 years on ART in the black population group indicating attainment of HIV uninfected mortality levels. However, in the non-black population group, relative risk was 1.59 [95% CI 1.30; 1.88] times higher than in the black population group which, while still within the insurance industry threshold, is higher than HIV uninfected levels of mortality. A further sub- analysis showed that while the immunological and virological response to ART was similar to that reported by the ART-CC in Europe, the level of relative risk was similar only in the non- black population group and the effect of current age on relative risk was strongly modified by population group.

Conclusions: The vast majority of this cohort of South African HIV-infected adults starting ART have both insurable levels of relative risk and comparable relative risk to DM2 when measured from multiple time points on ART by baseline and current characteristics. The only subgroup with relative risk exceeding the insurance industry threshold were patients with current CD4 counts < 200 cells/μl and unsuppressed viral loads (> 400 copies/ml). Mortality in the vast majority of this cohort attained CD4 counts $\geq$ 200 cells/μl and suppressed viral loads ($\leq$ 400 copies/ml) and approached HIV-uninfected levels after 3 years on ART. A novel analytics method is presented for modelling relative risk that better meets insurers' needs than existing studies reporting relative risk in defined intervals of ART using dated patient characteristics.