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Louis I. and Thomas D. Dublin Award 2023 Application

Statement of the Research

For consideration of the Dublin Award, I would like to submit my ongoing research entitled, **“Effectiveness of dolutegravir-based therapy compared to standard of care among children and adolescents living with HIV in South Africa, Mozambique, Tanzania, and Zimbabwe”**

This research study aims to **transport the primary efficacy results of the ODYSSEY Trial** (Once-Daily Dolutegravir-based antiretroviral therapy in Young people vS. Standard thErapY) to all children and adolescents aged 18 and younger living with HIV weighing 14 kg or more in four high HIV burden countries: South Africa, Mozambique, Tanzania, and Zimbabwe.

Since 2019, the **World Health Organization (WHO) has recommended countries use dolutegravir as the preferred first-line antiretroviral therapy for all age groups** (1). Several meta-analyses have demonstrated that dolutegravir-based therapies were more efficacious than non-nucleoside reverse transcriptase inhibitor (NNRTI)-based and protease inhibitor-based therapies for adults, with the odds of achieving viral suppression being around twice as high until 96 weeks after initiation (2–4).

The efficacy and safety of dolutegravir for children and adolescents living with HIV was shown by the ODYSSEY trial: the proportion of children and adolescents living with HIV weighing at least 14 kg (31 lb) with treatment failure was 8 percentage points lower (95% CI: 3 to 14) than standard of care, and the proportions of adverse events reported were not greater than standard of care (5).

Most high burden HIV countries have adopted dolutegravir for all ages as of June 2022 but some countries have yet to approve pediatric formulations for children weighing less than 20 kg (6). Two countries, South Africa and Mozambique, have yet to approve pediatric formulations while two other countries, Tanzania and Zimbabwe, have recently approved dolutegravir for all ages. Altogether, they account for 40% of the global population of 2.7 million children and adolescents living with HIV.

As WHO retains their recommendation on the use of dolutegravir-based therapies, **policymakers need to know how many children and adolescents living with HIV are going to benefit from a country-wide transition to dolutegravir-based therapy.** This efficacy estimate should account for the specific distribution of age, sex, weight, and prior treatment experience of that country, and that distribution is not the same as in the trial. Trials in general tend to over-enroll selected participants to have sufficient power to study key potential effect modifiers. **A more precise efficacy estimate helps in cost-effectiveness analyses weighing competing priority interventions, and helps in simplifying HIV program management, especially in the context of second- and third-line treatment.**

To answer this policy question, there is a need to bring together multiple data sources and advanced epidemiologic and biostatistical methods, specifically in the field of generalizability. Aside from trial data, data on the target population are also needed. In the past, studies that employ generalizability methods (e.g. (7–9)) use target population data from a disease registry or cohort study. However, it is infeasible in most contexts to maintain either, but disease burden estimates are still necessary for health policy and planning. **Therefore, a large majority of global estimates of disease burden are modeled or simulated,** and this is true for estimating global, regional, and country-specific populations of children and adolescents living with HIV. Therefore, beyond HIV programs, **this study also hopes to extend statistical methods on causal estimation in generalizability by incorporating uncertainty coming from modelling the target population.**

The simulated target population comes from the Joint United Nations Program on HIV/AIDS (UNAIDS) Spectrum model. Input parameters in the model come from reported estimates from country HIV surveillance and program data or are derived as a consensus among country experts (10).

The ODYSSEY trial results will be mapped to the target population using inverse odds of selection weights (7,8). In this approach, the weighted trial sample resembles the target population according to the distribution of covariates included in the weights. The inverse odds of selection weights are defined as a function of the odds of selection into the trial conditional on measured characteristics that define differences between the trial and target population and across which the effect of treatment is heterogeneous (7). **The inverse odds of selection weights will be estimated using a logistic regression model for sample membership (ODYSSEY versus target population) conditional on the following covariates:** sex at birth, age, weight, CD4 count and viral load at treatment initiation, and randomization stratification factors (first-/second-line treatment, routine availability of viral resistance testing, and intended nucleoside reverse transcriptase inhibitor (NRTI) backbone). **The estimated inverse odds of selection weight for each trial participant will be used as weights in the primary analysis estimating the treatment effect.**

The goal is to estimate the population average treatment effect in the target population by reweighting the analysis that estimated the sample average treatment effect in the trial population. The expectation is that the reweighted sample average treatment effect is an unbiased estimate of population average treatment effect assuming that the inverse odds of selection weight model was correctly specified with no measurement error, the trial participants were independently sampled, the treatments being considered in the study sample are also those considered in the target population (consistency), a non-zero probability of selection exists for each stratum of the measured characteristics (sample positivity), and the members of the target population selected and not selected in the study sample are similar across measured characteristics (conditional exchangeability) (10).

The primary analysis will estimate the risk difference of virological treatment failure at 96 weeks from treatment initiation or switching. The exposure variable is dolutegravir-based therapy, defined as dolutegravir and two nucleoside reverse transcriptase inhibitors (NRTI) as backbone. The comparator is standard of care, based on the clinician's decision at the time of randomization. **Survival curves will be estimated using weighted Nelson-Aalen curves,** and the risk difference of virological treatment failure comparing the dolutegravir and standard of care groups will be calculated from these curves (11,12). **Hazard ratios will be estimated from weighted Cox proportional hazards models. Because generalizability bias is scale-dependent, we will calculate the generalized effect on both absolute and relative scales.** The 95% confidence intervals will be calculated through bootstrapping methods with 1,000 sample replicates (13).

I anticipate that there will be some challenges meeting the positivity assumption, especially among those in the youngest age group (< 2 years), and the target population will be refined to account for these limitations. There are also challenges on extracting the full joint distribution of some effect modifiers in the target population, i.e. treatment experience, CD4 count, and viral load, so a range of assumptions on how they covary in the target population will be incorporated in sensitivity analyses.

In summary, this research study embodies the joint epidemiology-biostatistics focus of this award. **From an epidemiological perspective, this study extends the utility of an important clinical trial from individual to population-level efficacy, which in turn enhances HIV program management in children and adolescents living with HIV. From a biostatistical perspective, this study refines the precision of causal estimands in generalizability and extends the application of generalizability to target populations that are simulated.**

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