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Association Between Antiretroviral Treatment Regimen and Tuberculosis Preventative Treatment Completion for HIV-Positive Patients in Botswana

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Association Between Antiretroviral Treatment Regimen and Tuberculosis Preventative Treatment Completion for HIV-Positive Patients in Botswana

A thesis submitted in partial satisfaction

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by

Pranav Prathap Shetty

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ABSTRACT OF THE THESIS

Association Between Antiretroviral Treatment Regimen
and Tuberculosis Preventative Treatment Completion
for HIV-Positive Patients in Botswana

by

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Master of Science in Epidemiology
University of California, Los Angeles, 2021
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Tuberculosis (TB) is a major global health concern and is responsible for significant morbidity and mortality, especially among people living with HIV (PLHIV). TB preventative therapy using isoniazid (IPT) for latent TB in PLHIV is a commonly recommended, although often underutilized, treatment to decrease progression to active disease, as well as reduce the possibility of onward disease transmission. This study investigates factors associated with IPT course completion in a large cohort of PLHIV in Botswana, focusing on the antiretroviral (ARV) therapy a patient is receiving. 57,359 PLHIV were evaluated for IPT, 40,379 (70.4%) patients initiated IPT, and 38,293 (94.8%) of these completed the course of therapy. Logistic regression modelling was used to evaluate the association between ARV regimen, as well as other independent variables of age, gender, pregnancy status, and daily pill burden, with the dependent outcomes of IPT completion, IPT initiation, side effects, and death. We found that certain ARV regimens were associated with

the likelihood of IPT completion; when compared to the reference ARV of TDF/FTC/EFV, TDF/3TC/DTG was found to be associated with an increased likelihood of treatment completion (OR = 1.24; 95% CI = 1.08, 1.43), while AZT/3TC_EFV (OR = 0.75, 95% CI = 0.62, 0.90), AZT/3TC_NVP (OR = 0.82, 95% CI = 0.68, 1.00), and TDF/FTC_LPV/R (OR = 0.70, 95% CI = 0.51, 0.98) were found to be associated with a decreased likelihood of treatment completion. Part of this relationship is possibly secondary to the daily pill burden of those ARV regimens, as well as side effects that may occur with concomitant IPT. Additionally, ARV regimen, age, and gender, were found to be associated with initiation of IPT, suggesting that targeted educational interventions may be needed in specific groups to increase participation in IPT programs. These findings should be taken into consideration by clinicians and managers intending to increase the operational effectiveness of IPT programs.

The thesis of Pranav Prathap Shetty is approved.

Robert Kim-Farley

Sanghyuk Shin, Committee Co-Chair

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Introduction:

Tuberculosis (TB) has killed more humans than any other infectious disease in recorded history; it has been estimated that TB can be held responsible for a billion lives lost over the past 200 years.[1] In 2019, approximately 10 million individuals were newly infected with TB and 1.4 million died from TB disease; this includes 200,000 people who were also coinfected with human immunodeficiency virus (HIV). TB is often thought of as a disease of antiquity, yet it continues to present itself as a modern public health concern. It is currently the leading cause of death globally from a single infectious agent and is the number one cause of death overall for people living with HIV. Fundamentally, TB is a disease of poverty, vulnerability, and inequity and while just thirty of the high TB burden countries account for over 90% of disease worldwide, TB has the potential to affect anyone on the planet. Consequently, it is incumbent on national health systems, supported by the international community, to address this collective and persistent threat.[2]

The World Health Organization (WHO) End TB Strategy, adopted by all member states of the WHO in 2014 and officially launched in 2015, calls for an 90% reduction in TB incidence and a 95% reduction in TB deaths worldwide by 2035; an ambitious target which is well-aligned with the United Nations Sustainable Development Goals. This strategy is supported by three pillars: 1) Integrated patient-centered care and prevention; 2) Bold policies and supportive systems; and 3) Intensified research and innovation.[3] TB prevention plays a pivotal role, especially among those at greatest risk of TB disease, such as people living with HIV (PLHIV). In 2018, the first-ever United Nations High-Level Meeting on the Fight Against Tuberculosis convened, further reaffirming the WHO End TB Strategy, and set bold new targets on the provision of TB preventative therapy for 30 million people globally, including 4 million children under 5 years of age, 20 million household contacts, and 6 million PLHIV, by 2022.[4] Coordinated and focused efforts at a national level are required to create the supply and logistical infrastructure, a

supportive policy environment, and the human and intellectual capital needed to allow for early diagnosis as well as curative and preventative treatment of TB.

The natural history of TB begins with the entry of *Mycobacterium Tuberculosis* bacteria into the lungs of a susceptible host, primarily through droplet or airborne transmission originating from an individual with active pulmonary TB disease. Subsequently, this results in one of three main outcomes: the host innate immune response either clears the infection; contains the infection (also known as latent TB); or is overwhelmed by the infection and active pulmonary or extra-pulmonary TB disease develops. The final pathway depends on a variety of factors which are still under active investigation, but include the infectious dose, the age and immune competency of the host, and the presence of previous pulmonary disease, among several others. The likelihood of infection also depends on the severity of disease in the index patient, the duration and intensity of exposure, and the quality of ventilation and ultraviolet light exposure in any shared space.[5]

One of the greatest challenges inherent to TB control is that of latent infection; this occurs when the disease lays dormant in an individual, avoiding the immune system for years or decades, and causing no apparent symptoms in the host. As such, latent tuberculosis infection (LTBI) is extremely challenging to diagnose given that the patient is generally unaware that they have been infected. LTBI is traditionally defined as evidence of persistent TB infection without clinical manifestations of the disease; however more recent research describes latent TB as a spectrum of truly quiescent disease to one of slow and ongoing replication in the lungs. LTBI infection is most commonly confirmed by assessing immune reactivity to *Mycobacterium Tuberculosis* organisms through tuberculin skin testing (TST) or interferon-gamma release assay (IGRA) testing performed on serum. While LTBI does represent an ongoing TB infection in the host, those with LTBI cannot spread the disease to others. Although the global burden of LTBI is not known

with certainty, it is estimated that over two billion people, over a quarter of the world's population, are harboring latent TB, a vast hidden reservoir.[6]

LTBI carries an overall 5% - 10% lifetime risk of progressing to active TB, most commonly occurring within the first two years; this risk is substantially increased in cases of immunosuppression, such as which exists in individuals whom are coinfected with HIV. People living with HIV (PLHIV) are one of the foremost populations which are most at risk due to compromised cell-mediated immunity and are estimated to be 20-fold more likely to develop active TB than those without HIV; this translates to a 10% risk per year of progressing to active TB disease. This is thought to be secondary to two major mechanisms: increased susceptibility to initial TB infection and increased likelihood of reactivation of latent TB infection. It is well-established that both antiretroviral treatment (ART), as well as treatment of LTBI in HIV-positive patients, leads to decreased progression to active TB, decreased mortality from TB disease, and ultimately, decreased overall TB transmission.[7] As such, a major component of global TB control hinges on identifying and treating LTBI within PLHIV.

Tuberculosis preventative treatment (TPT) is recommended by the WHO for all PLHIV over the age of 1 year regardless of prior TB treatment, CD4 count, pregnancy status, or current antiretroviral treatment. In the case of infants (less than 12 months of age) living with HIV, TPT is recommended if there is additionally a household contact with active TB disease.[8] The 2018 Lancet Commission on Tuberculosis, "Building a Tuberculosis-free World", posits that TPT represents one of the most efficacious interventions to reduce TB incidence and is a critical component of global TB control.[9] There are numerous pharmacologic treatment options for TPT, almost all of which utilize a particular combination of isoniazid, rifapentine, or rifampicin, either concurrently or as a single agent, for a period of one to nine months depending on drug availability and the level of risk of progression to active TB. Due to the potential for inducing anti-microbial

resistance, active TB disease must be excluded prior to starting TPT; this is generally performed through symptom-based screening followed by a nucleic acid amplification test (Xpert MTB/RIF) and/or chest radiography if indicated. Following exclusion of active TB disease, TPT may be initiated and patients should be routinely monitored for adherence to therapy as well as adverse events throughout their treatment course, the most serious of which is drug-induced hepatotoxicity.[8]

One of the most common WHO-recommended medication regimens for TPT in PLHIV utilizes isoniazid monotherapy (IPT) for six months; IPT has been previously shown to provide added protection against the development of active TB when combined with ART as well. In low-TB transmission settings, IPT has resulted in a long-term protective benefit against TB disease in addition to a decrease in overall mortality. This was particularly demonstrated in the follow up to the Temprano ANRS 12136 trial conducted in Cote d'Ivorie which revealed a 37% reduction in all-cause mortality six years post-IPT.[10] However, this benefit is not necessarily borne out in high-TB transmission settings. Studies conducted in Botswana[11] and South Africa[12] suggest that during the period of IPT, TB incidence decreased between 32% - 58%, but this benefit was rapidly lost after cessation of treatment; this was possibly due to a new infection with TB after the protective effect of IPT waned. These findings provide support to the notion that in settings of high TB transmission, continuous isoniazid therapy may be of further benefit for PLHIV.[13]

While TPT is currently recommended for all PLHIV, drug-drug interactions need to be carefully evaluated due to patients being treated with concomitant, and often complicated, ART regimens. IPT is not thought to have any significant pharmacologic interactions with any presently recommended ART regimens and carries a low overall risk of toxicity; the most common side effects include drug-induced hepatitis, peripheral neuropathy, and cutaneous rash.[14] The predominant disadvantage of IPT is the long (6 month-plus) treatment course which may limit

adherence as shorter courses of therapy have been shown to be related to increased compliance.[15] However, given the importance of adherence to therapy and treatment completion to providing maximal protection from TB infection, as well as minimizing the potential development of anti-microbial resistance, the investigation of factors that are associated with treatment completion is a critical exercise.

In Botswana, the true prevalence of TB infection is unknown; the first ever national TB prevalence survey is planned for 2021, although the recent and ongoing COVID-19 global pandemic may result in delays to implementation. In 2019, an estimated 5,800 individuals developed active TB disease (new or relapse), an incidence rate of 235 per 100,000 persons; the total population of Botswana is approximately 2.3 million. Among all estimated active TB cases, the percent that were HIV positive was 42%.[2] Botswana also carries one of the highest per-capita HIV burdens worldwide; the HIV prevalence rate among adults aged 15 to 49 is estimated to be 20.7% with 380,000 currently living with HIV. Of the 14,713 individuals newly enrolled in HIV care in 2019, 1,399 were found to have active TB disease, 9.5% of the total.[16] As such, Botswana is considered by the WHO to be one of the 30 combined HIV/TB high-burden countries necessitating proactive management of both diseases.

The Ministry of Health and Wellness in Botswana recently initiated a Tuberculosis Preventative Therapy program through general outpatient clinics (OPD), Infectious Disease Care Clinics (IDCC), and US Presidents Emergency Plan for AIDS Relief (PEPFAR)-funded clinics for HIV-positive patients. This program began in August 2019 and in keeping with national and WHO recommendations, its' purpose is to systematically screen all HIV-positive patients for eligibility for TPT through a facility-based approach, to initiate TPT therapy for eligible patients, and to monitor progress monthly throughout the program until completion of therapy. The therapeutic course currently being utilized in this program consists of IPT for six months. As of December

2020, over 57,000 patients have been screened for IPT eligibility and over 40,000 patients have initiated IPT.

While several prior studies have described varying completion rates for IPT programs ranging from 75% - 97% in diverse settings[17,18,19,20], there has not been a study published to date that has investigated the association between a specific ART regimen and IPT initiation and completion rates. While there is no known pharmacologic drug-drug interaction between the various currently utilized ART regimens and isoniazid, the existence of synergistic side effects or overall daily pill burden associated with different ART regimens may impact treatment compliance in particular individuals. Previous studies in Botswana specifically looking at the side effect of isoniazid-induced hepatitis with smaller cohorts have found higher rates among those receiving ART, particularly with nevirapine, although these associations were not statistically significant[21] and overall pill burden in patients taking ART has been previously shown to be associated with lower rates of adherence.[22]

The objective of this study is to utilize the operational and clinical dataset from the Botswana TPT program, which was obtained under routine programming conditions, in order to evaluate the association between ART Regimen and IPT completion in this cohort of PLHIV; the rate of IPT initiation, the incidence of side effects and death, and the effect of pregnancy was also investigated. Given that the initiation of TPT would add additional daily pills for the patient to take, the association between existing ART daily pill burden and the outcome measures was also examined. As completion of IPT is crucial for decreasing the future incidence of TB disease, curtailing ongoing TB transmission, and decreasing overall mortality for PLHIV, we hope these findings will supplement the literature base of how to optimize the operational effectiveness of TPT programs.

Methods:

Study Setting and Program Description:

The TPT program in Botswana was initiated in 2019 within 41 clinics across 11 geographical districts following the guidelines previously established in the Handbook of the Botswana 2016 Integrated HIV Clinical Care Guidelines.[23] This IPT program utilizes isoniazid (5mg/kg for adults, 10mg/kg for children, max dose of 300mg daily) combined with pyridoxine (25 mg daily) to minimize the occurrence of peripheral neuropathy that is common with isoniazid therapy alone. Routine tuberculin skin testing or chest x-ray to confirm LTBI was not required. Inclusion criteria for the IPT program included: 1) All PLHIV over 12 years of age; 2) All children between the ages of 5 years and 12 years of age whom are living with HIV and have had contact with a confirmed TB case; and 3) All children under 5 years of age have had contact with confirmed TB case regardless of their HIV status

Figure 1 depicts a flowchart of the clinical selection process. In brief, patients who met the inclusion criteria were then assessed for symptoms of active TB (cough, fever, weight loss, night sweats, lymphadenopathy, and decreased playfulness for children). If positive, patients were investigated for active TB through bacteriologic testing. If screen-negative for clinical symptoms of active TB, and in those whom were screen-positive but tested negative for active TB by bacteriologic evaluation, patients were then assessed for specific contraindications to IPT. Contraindications included acute or chronic hepatitis, known hypersensitivity to isoniazid, peripheral neuropathy, regular or heavy alcohol use, or if anti-retroviral (ARV) medications were also changed on that visit. Midway through the program, positive pregnancy status was added as an additional contraindication to TPT. If no contraindications were present, the patient was deemed eligible for TPT. IPT was offered/initiated and the patient was monitored monthly until completion of the 6-month course of medication. For study purposes, outcomes were grouped

into the following categories: Completion of IPT; Death; Suspension of IPT due to Side Effects; and Other.

Study Design:

This is a prospective study investigating a fixed cohort of patients participating in the Botswana TPT program between August 2019 and December 2020. The patients were identified through active screening at the point of entry to selected health facilities and all enrolled patients were entered into a cohort database which was primarily used for operational and clinical monitoring purposes. The database contains longitudinal information for every patient visit and re-visit to the clinic. If a patient was started on IPT, follow-up information collection was concluded at the time the patient either completed or discontinued therapy up to a maximum of 6 months after IPT initiation.

Data Management:

Data were initially collected in RedCap, exported to Excel, and then imported and analyzed using R, Version 4.0.2. Data collected included patient demographic information (birth date and gender); the clinic the patient visited and the respective geographical district; HIV status and current ARV Regimen; Active TB symptom assessment and outcome of TB investigation process; presence of contraindications; pregnancy status at time of screening; eligibility and ITP initiation status; reasons for non-initiation of IPT; side effects experienced by those who started ITP; outcome of ITP and reason of discontinuation of therapy; as well as other clinical and programmatic variables not utilized in this study. For the purposes of this study, patients in whom HIV status was negative or unknown were excluded from analysis.

Data cleaning and recategorization of variables was performed to allow for statistical analysis procedures. Due to several instances of missing data field entries, measured assumptions were

made to reconcile specific discrepancies. These included: 1) Patients were categorized as HIV-positive if they were marked as such or if they were marked as being on any ART regimen; 2) Age was calculated as the time between the listed birth date and the entered date of initial screening and any negative or zero values were marked as missing; 3) Patients were categorized as starting IPT if they were marked as such or if they had any outcome of IPT listed; and 4) Patients were categorized as eligible for IPT if they were marked as such or if they were categorized as starting IPT. The total number of clinics in the initial database was 41; clinics that had less than 700 assigned patients were collapsed into a single category resulting in a total of 33 discrete clinic locations.

Daily pill burden was defined as the total number of pills per day each ART regimen necessitated. In this patient cohort, those on TDF/FTC/EFV and TDF/3TC/DTG took 1 pill per day; those on TDF/FTC_NVP and ABC/3TC/DTG + TAF/ED took 2 pills per day, and those on AZT/3TC_EFV, AZT/3TC_NVP, and TDF/FTC_LPV/R took 3 pills per day. Pill burden was not calculated for those on ART Regimens categorized as “Other” as this would vary based on specific regimen.

ARV Regimen	Number of Pills	Daily Frequency	Total Pills per Day
TDF/FTC/EFV	1	1 pill once	1
TDF/3TC/DTG	1	1 pill once	1
TDF/FTC_NVP	2	1 pill once	2
ABC/3TC/DTG + TAF/ED	2	1 pill once	2
AZT/3TC_EFV	2	1 pill once, 1 pill twice	3
AZT/3TC_NVP	2	1 pill once, 1 pill twice	3
TDF/FTC_LPV/R	2	1 pill once, 1 pill twice	3

Statistical Analysis:

Descriptive statistics were calculated for the overall patient population screened and were disaggregated by IPT initiation status. The number of patients who completed each step of the IPT program was determined. This included: 1) Number initially assessed for IPT eligibility; 2) Number eligible for IPT initiation after screening for active TB and the presence of contraindications; 3) Number who initiated IPT; and 4) Number who completed IPT, died, or experienced side effects that led to discontinuation of IPT. Outcome of IPT in the database was defined as one of 10 potential results: 1) Completion of IPT course; 2) Death (any cause); 3) Lost to Follow-Up; 4) Patient deferral; 5) Clinician deferral; 6) Poor adherence; 7) Side effects; 8) Active TB; 9) IPT Declined after initiation; 10) Other.

The primary outcome of interest in this study was completion of the IPT course among all those who initiated IPT; all other outcomes of IPT as listed within the database were considered to indicate non-completion of therapy. Secondary outcomes in this study included 1) IPT Initiation among all patients; 2) Death among those who initiated IPT; and 3) Side Effects that led to discontinuation of therapy among those who initiated IPT. The primary independent variable of interest was the current ARV Regimen the patient was being administered. Additional independent variables included: 1) Patient Age; 2) Patient Gender; 3) Pregnancy Status; 4) Daily ARV Pill Burden; and 5) Treatment Clinic.

Continuous variables were summarized using means and standard deviations while categorical variables were summarized using absolute values and frequencies. Logistic regression models were run to estimate the association between ART regimen and IPT course completion while controlling for potential confounding variables including the specific clinic attended, age, and gender; the effect of pregnancy was only investigated within female patients. While clinic location was considered an independent variable in all regression models, it was treated primarily as a co-

variable in the fully-adjusted models and not as a potential determining factor for the listed outcomes. Models investigating the association between pill burden and outcome did not include ART regimen as a co-variable to minimize the potential for collinearity and were run independently. Separate logistic regression models were constructed for the secondary outcomes of IPT initiation, death, and side effects as dependent variables and were analyzed using the same methodology. Pregnancy status was not included in the analysis of IPT initiation due to the change of eligibility criteria for IPT partway through the program.

Mixed-effects logistics regression models were additionally investigated due to the potential of clustering and non-independence of outcome based on the particular clinic an enrolled patient visited; these results were compared to those of the fixed-effects regression model in order to determine the optimal prediction model. For all outcomes, the fixed-effect logistic regression model produced a similar estimate of association to the mixed-effect regression model with a lower Akaike Information Criterion (AIC) number and so fixed-effect logistic regression models were utilized for final analysis. For all multivariate models, the variance inflation factor (VIF) was calculated to assess for the potential for multicollinearity and the Hosmer-Lemeshow Goodness of Fit test was utilized to assess the logistic regression model fit.

Ethical Approval:

This study was approved by the Botswana Ministry of Health Human Research Development Committee. Informed consent was not obtained from patients as this study involved analysis of routine programmatic data and no specific patient identifying information was available within the dataset or to study investigators.

Results:

Study Participant Characteristics:

Figure 2 shows a schematic of the study outcomes flowchart. 57,375 patients in total were screened for eligibility for IPT across 41 clinics; of these, 57,359 (99.97%) were HIV-positive and met criteria for inclusion in the study. Within the study population, 36,604 (63.8%) were female, 20,755 (36.2%) were male, and the average age was 43.2 years of age (SD = 11.95 years). 45,144 (78.7%) of all included patients were found to be eligible for IPT due to lack of symptoms of active TB, as well as the absence of contraindications; of these, 40,379 (89.5%) patients initiated IPT. 38,293 (94.8%) of all patients that initiated IPT successfully completed the prescribed 6-month course of medication. 45 (0.11%) died during the 6-month follow-up period after IPT initiation, and 694 (1.72%) discontinued IPT due to the occurrence of side effects. 1,347 (3.34%) patients had other outcomes listed without recorded completion of therapy.

Figure 3 shows the distribution of all contraindications for the 2,673 patients for which specific data were available. Overall, 12,215 patients were excluded from initiating IPT due to the presence of clinical contraindications; the specific reason for the contraindication was listed for 2,673 patients and was unavailable in the database for 9,542 patients. Of those with listed contraindications, the most common reasons included pre-existing peripheral neuropathy in 801 patients (30.0%); ARV drugs were switched on same day as IPT screening in 607 patients (22.7%); Regular or heavy alcohol consumption in 503 patients (18.8%); and Active TB disease in 322 patients (12.1%). Figure 4 shows the distribution of all deferrals for the 3,511 patients for which specific reasons for deferral were available. Of the 45,144 patients that were eligible for IPT, 4,765 deferred therapy and the general reason for non-initiation of therapy was available for 4,624 patients. 4,464 (93.7%) declined to take IPT after being offered therapy or deferred the decision until a later date, and in a small minority of cases (160 patients, 3.4%), the treating doctor was unaware of the recommendation and/or protocol for IPT implementation for the patient.

Table 1 shows the distribution of additional associated patient characteristics including pregnancy status, geographic district of the treating facility, ARV regimen, and daily ARV pill count, disaggregated by IPT initiation status. The mean age of those patients who initiated IPT (43.5 years) was similar to those that did not (42.6 years). Overall, 848 (2.3%) female patients were pregnant at the time of screening and the percentage of those who started IPT whom were pregnant (1.8%), was less than half of those who did not start IPT (3.8%). The plurality of patients originated from District 15 (46.2%), followed by District 16 (19.9%), and District 3 (8.9%). In terms of current ARV regimen, most patients were prescribed either TDF/FTC/EFV (34.2%) or TDF/3TC/DTG (33.5%), followed by AZT/3TC_EFV (9.4%), AZT/3TC_NVP (9.2%), and TDF/FTC_NVP (6.2%). Most patients were on an ARV regimen that necessitated one pill per day (69.7%), followed by three pills per day (21.3%), and then two pills per day (9.0%).

Primary Outcome - IPT Completion:

Table 2 shows the odds ratios and 95% confidence intervals derived from the bivariable logistic regression analyses performed in order to evaluate the association between the dependent variable (IPT completion) and the various independent variables (Age; Gender; ARV regimen) within the subgroup of patients who initiated IPT (N = 40,379). Older age was found to be associated with a decreased likelihood of treatment completion (OR = 0.988; 95% CI = 0.984, 0.992). Treatment completion occurred in 95.7% of females and 95.6% of males; Gender (reference category = female) was not found to be associated with treatment completion (OR = 0.982; 95% CI = 0.888, 1.09). Of the 33 treating clinics (reference = Princess Marina Hospital, the main public hospital in the capital Gaborone), treatment completion ranged from 85.2% to 99.4%. Twenty-nine treating clinics were found to be associated with an increased likelihood of treatment completion and one was found to be associated with a decreased likelihood of treatment completion when compared to Princess Marina Hospital. For ARV regimen (reference = TDF/FTC/EFV), treatment completion ranged from 96.65% with TDF/3TC/DTG to 92.06% with

TDF/FTC_LPV/R. TDF/3TC/DTG was the only ARV regimen found to be associated with an increased likelihood of treatment completion (OR = 1.21; 95% CI = 1.06, 1.39) when compared to TDF/FTC/EFV. With the exception of TDF/FTC_NVP, which did not have a statistically significant association, all other ARV regimens were found to be associated with a lower likelihood of treatment completion when compared to TDF/FTC/EFV.

Table 2 also includes the odds ratios and 95% confidence intervals derived from the multivariable logistic regression analysis. In this multivariable adjusted model, Age (OR = 0.99, 95% CI = 0.99, 1.00) and male gender (OR = 1.05, 95% CI = 0.93, 1.18) were not found to be statistically associated with the likelihood of IPT completion. TDF/3TC/DTG was the only ARV regimen found to associated with an increased likelihood of treatment completion (OR = 1.24; 95% CI = 1.08, 1.43), while AZT/3TC_EFV (OR = 0.75, 95% CI = 0.62, 0.90), AZT/3TC_NVP (OR = 0.82, 95% CI = 0.68, 1.00), and TDF/FTC_LPV/R (OR = 0.70, 95% CI = 0.51, 0.98) were found to be associated with a decreased likelihood of treatment completion as compared to TDF/FTC/EFV. 29 clinic locations were found to be statistically associated with an increased likelihood of treatment completion while only one clinic was found to be associated with a decreased likelihood of treatment completion when compared to Princess Marina Hospital.

Table 2 additionally shows the odds ratios and 95% confidence intervals from the separate bivariable and multivariable regression models run to evaluate the association between pregnancy status and daily pill burden on the dependent variable (IPT completion) while controlling for all other independent variables. Of the 26,265 female patients who started IPT, 459 were pregnant at the time of screening and 425 completed IPT (92.6%); the reference pregnancy status for the regression model was non-pregnant. While females who were pregnant trended toward a lower likelihood of treatment completion in the bivariate model, this did not reach statistical significance (OR = 0.707, 95% CI = 0.485, 1.07, p = 0.082). The multivariable logistic

regression model which controlled for age, ARV regimen, and treatment clinic did not find a statistically significant association between pregnancy status and treatment completion (OR = 0.905, 95% CI = 0.591, 1.457). In terms of daily pill burden (reference category = 1 pill per day), the bivariable logistics regression model found that a pill burden of two pills per day (OR = 0.691, 95%CI = 0.580, 0.828), as well as three pills per day (OR = 0.583, 95%CI = 0.517, 0.695), were significantly associated with lower likelihood of IPT completion. In the multivariable adjusted model which controlled for age, gender, and treatment clinic, a pill burden of two pills per day (OR = 0.824, 95%CI = 0.685, 0.997), as well as three pills per day (OR = 0.706, 95%CI = 0.617, 0.810), were again found to be significantly associated with lower likelihood of IPT completion.

Secondary Outcome - IPT Initiation:

Table 3 shows the odds ratios and 95% confidence intervals derived from the bivariable and multivariable logistic regression analyses performed in order to evaluate the association between the dependent variable (IPT initiation) and the various independent variables (Age; Gender; ARV regimen) within all the patients that were included in the study (N = 57,359). In both unadjusted and adjusted models, older age was found to be statistically associated with an increased likelihood of treatment initiation. Gender (reference category = female) was also found to be associated with the likelihood of treatment initiation with males having lower rates of IPT initiation as compared to females in both models. Of the 33 treating clinics, 30 clinics in the bivariable model and 22 clinics in the multivariable model were found to be associated with an increased likelihood of treatment initiation when compared to Princess Marina Hospital. For ARV regimen (reference = TDF/FTC/EFV), treatment initiation rates ranged from 61.5% with Other ARVs to 80.4% with ABC/3TC/DTG + TAF/ED. In the unadjusted analysis, TDF/3TC/DTG and ABC/3TC/DTG + TAF/ED were found to be associated with an increased likelihood of treatment initiation when compared to TDF/FTC/EFV while all other regimens were found to be statistically associated with a lower likelihood of treatment initiation. In multivariable modeling, TDF/3TC/DTG

was not found to be associated with the likelihood of treatment initiation while all other ARV Regimens were associated with a lower likelihood of treatment initiation as compared to TDF/FTC/EFV.

Table 3 additionally shows the odds ratios and 95% confidence intervals from the bivariable and multivariable regression models run to evaluate the association between daily ARV pill burden (reference category = 1 pill per day), on the dependent variable (IPT initiation) while controlling for all other independent variables. The bivariable logistics regression model found that a pill burden of two pills per day (OR = 0.839, 95%CI = 0.779, 0.905), as well as three pills per day (OR = 0.754, 95%CI = 0.716, 0.795), were significantly associated with lower likelihood of IPT initiation. In the multivariable adjusted model which controlled for age, gender, and treatment clinic, a pill burden of two pills per day (OR = 0.721, 95%CI = 0.663, 0.784), as well as three pills per day (OR = 0.743, 95%CI = 0.700, 0.790), was again found to be significantly associated with a lower likelihood of IPT initiation

Secondary Outcome - Death:

Table 4 shows the odds ratios and 95% confidence intervals derived from the bivariable and multivariable logistic regression analyses performed in order to evaluate the association between the dependent variable (Death on IPT) and the various independent variables (Age; Gender; ARV regimen; Pregnancy status; Daily ARV pill burden) within the subgroup of patients who initiated IPT (N = 40,379). In bivariable analysis, older age was found to be statistically associated with an increased likelihood of death (OR = 1.046; 95% CI = 1.021, 1.071), while gender (reference category = female) did not show any association with death. One clinic was found to be associated with an increased likelihood of death (OR = 3.79; 95% CI = 1.00, 15.38); there was no other association found across the other clinics when compared to Princess Marina Hospital. For ARV Regimen, TDF/FTC_LPV/R (OR = 5.901; 95% CI = 1.32, 19.35) was found to be associated with

an increased likelihood of death during treatment when compared to TDF/FTC/EFV, while no other regimens were found to be have a statistically significant association.

In multivariable analysis, increasing age (OR = 1.061, 95% CI = 1.027, 1.095), one clinic location (OR = 9.486, 95% CI = 2.075, 51.037), and TDF/FTC_LPV/R (OR = 6.383, 95% CI = 1.323, 23.314) were again found to be associated with an increased likelihood of death during treatment. In this study, none of the 452 pregnant females who started IPT are known to have died during the six-month follow-up period; as such no regression modeling was performed. Daily ARV pill burden was not found to be significantly associated with death on IPT in both bivariable and multivariable models.

Secondary Outcome - Side Effects:

Table 5 shows the odds ratios and 95% confidence intervals derived from the bivariable and multivariable logistic regression analyses performed in order to evaluate the association between the dependent variable (Side effects leading to discontinuation of IPT) and the various independent variables (Age; Gender; ARV regimen; Pregnancy; Pill burden) within the subgroup of patients who initiated IPT (N = 40,379). In bivariable analyses, older age was found to be statistically associated with an increased likelihood of side effects (OR = 1.031; 95% CI = 1.024, 1.037), while gender was not found to have an association. Of the 33 treating clinics, all clinics except for one were found to be associated with a lower likelihood of side effects when compared to Princess Marina Hospital. For ARV Regimen, rates of side effects leading to discontinuation of treatment ranged from 1.03% with TDF/3TC/DTG to 3.87% with TDF/FTC_LPV/R. While TDF/3TC/DTG showed a statistically significant association with a lower likelihood of side effects when compared to TDF/FTC/EFV, all other ARV Regimens showed a statistically significant association for a higher likelihood of side effects. In multivariable analysis, increasing age (OR = 1.061, 95% CI = 1.027, 1.095) was again found to associated with increased likelihood of side

effects causing discontinuation of treatment, while was no relationship found between side effects and gender. AZT/3TC_EFV, AZT/3TC_NVP, and ABC/3TC/DTG + TAF/ED were found to be associated with an increased likelihood of side effects causing discontinuation of treatment while there was no association found with the other ARV Regimens as compared to TDF/FTC/EFV.

Females who were pregnant had a higher likelihood of experiencing side effects (OR = 2.332, 95% CI = 1.392, 3.660) in the bivariable model, although in the multivariable model, pregnancy trended toward a higher likelihood of side effects, but this did not reach statistical significance (OR = 1.712, 95% CI = 0.9513, 2.862, p = 0.054); overall 18 of the 459 pregnant females stopped IPT due to side effects (3.92%). In terms of daily pill burden, two pills per day (OR = 1.953, 95%CI = 1.484, 2.536), as well as three pills per day (OR = 2.726, 95%CI = 2.277, 3.260), were found to be significantly associated with side effects on IPT compared to an ARV regimen of one pill per day. This association was upheld in the multivariable model as well; two pills per day (OR = 1.417, 95%CI = 1.061, 1.868), as well as three pills per day (OR = 1.790, 95%CI = 1.463, 2.189) were again found to be significantly associated with higher likelihood of side effects leading to discontinuation of IPT.

For all multivariable regression analyses, the VIF and Hosmer and Lemeshow Goodness of Fit test were run within each model. All models had a VIF < 1.62 indicating low likelihood of multicollinearity and a Hosmer and Lemeshow Goodness of Fit test p-value > 0.15 indicating low evidence for a poorly fitting model.

Discussion:

The objective of this study was to investigate factors associated with completion of TB preventative therapy using isoniazid for six months in a large cohort of PLHIV in Botswana; secondary outcomes including IPT initiation, death, and side effects resulting in cessation of therapy were also investigated. We found that the ARV regimen a patient was administered was associated with their overall likelihood of IPT completion, specifically that TDF/3TC/DTG was associated with an increased likelihood of treatment completion, while AZT/3TC_EFV and TDF/FTC_LPV/R were associated with a decreased likelihood of treatment completion as compared to the reference ARV of TDF/FTC/EFV. While the reasons for this association between ARV regimen and IPT completion could be myriad, two possibilities include the occurrence of side effects with certain ARV regimens versus others when combined with IPT and the effect of overall daily ARV pill burden on adherence.

Daily pill burden is a critical factor due to fact that PLHIV often have to take multiple different medications and previous studies have shown that increasing ARV pill burden is associated with decreased ARV treatment adherence.[24] This finding was also seen in our cohort where current daily ARV pill count was significantly associated with a decreased likelihood of IPT completion, as well as a decreased likelihood of IPT initiation, and an increased likelihood of side effects leading to discontinuation of IPT. Given the general challenge of medication adherence for patients with multiple daily medications, the addition of two medications for IPT (isoniazid plus pyridoxine) could impact overall medication adherence, including possibly ARV adherence (not measured in this study). Additionally, AZT/3TC_EFV, AZT/3TC_NVP, and ABC/3TC/DTG + TAF/ED were found to be associated with a higher likelihood of side effects while on IPT which possibly contributes to the decreased rate of IPT completion in AZT/3TC_EFV. As such, the individual ARV regimen for each patient should be considered when initiating IPT as additional interventions to increase adherence may be needed.

As compared to our study, previous studies in similar settings have shown widely varying results with regards to IPT completion. A IPT program in Tanzania found that 87% of patients completed IPT[25], while 91.7% of patients did so in Kenya[26], although other studies have shown markedly lower completion rates, including previous studies in Botswana (29.9%)[27], as well as in Nigeria (40.0%)[28]. Within these studies, there are several variables that may have impacted IPT completion rates that were not present to a high degree within our patient cohort and treatment setting. One of the most common reasons listed for non-completion of IPT in previous studies was drug stock-outs accompanied by an associated clinical fear of inducing isoniazid resistance due to incomplete therapy.[17,29] Significant patient loss to follow-up, poor integration of IPT programs with primary health care and HIV services, lack of clear treatment guidelines for clinicians, and younger patient cohorts additionally contributed to reduced IPT completion rates in previous studies.[30,31,32]

Within our cohort neither age or gender were associated with the likelihood of treatment completion, although in contrast, both age and gender were found to have significant associations with IPT initiation with increasing age being associated with increased likelihood of treatment initiation and male gender associated with a lower likelihood of IPT initiation. In Botswana the estimated percentage of PLHIV whom are female was 56.8% in 2019[33], while in this cohort the percentage of patients that initiated IPT whom were female was 65.0%. This gender difference in IPT initiation is consistent with previous studies[34,35] which have also shown lower rates of initiating IPT within males. Future educational interventions to reconcile this difference should be considered in relevant settings, such as community awareness campaigns targeting males in order to boost IPT enrollment.

ARV regimen also showed a significant association with IPT initiation, with all regimens except for TDF/3TC/DTG having lower rates of IPT initiation when compared to TDF/FTC/EFV;

TDF/3TC/DTG and TDF/FTC/EFV had no difference found between them with regards to initiation. While a previous study in Tanzania showed decreased rates of IPT initiation with concomitant ARV therapy overall[36], there was no further disaggregation of the specific ARV regimen. The reason for this association is unclear; possible reasons include overall daily pill burden, the association of a particular ARV regimen with a contraindication to IPT, the selection process which led to the choice of a specific ARV regimen, or other factors. Previous studies have shown that pregnancy results in a lower likelihood of IPT initiation[37,38]; this was not assessed in our dataset due to the programmatic change of eligibility criteria. Given that pregnancy is not thought to represent a contraindication to IPT, additional training to clinicians on IPT contraindications, as well as patients on the safety of IPT in pregnancy, may be warranted.

Increasing age was found to be associated with both death on IPT, as well as side effects leading to discontinuation of therapy, while there was no relation to gender. This is not surprising as increasing age generally correlates with an increased incidence of death, as well as possible side effects, often due to concomitant comorbidities and additional pharmacotherapy; increasing age has previously been shown to be correlated with an increased risk of adverse events with IPT.[39] None of the pregnant patients on IPT died during the study period and while pregnancy trended towards a higher likelihood of side effects, this did not reach statistical significance. TDF/FTC_LPV/R was the only ARV regimen found to be statistically associated with death on IPT; the reason for this association is unclear. A previous small study showed that while both isoniazid and LPV/R inhibited CYP450 processing enzymes in the liver, this did not result in altered pharmacodynamics of LPV/R.[40] This possible relationship between TDF/FTC_LPV/R and death on IPT should be investigated further in future studies. Of note, given the low number of deaths in this dataset, as well as the wide confidence intervals as shown in Table 4, these associations should not be taken as conclusive.

The strengths of this study include the analysis of a new IPT program in one of the largest cohorts of PLHIV reported in the literature to date using data that were collected under routine programming conditions, likely better reflecting real-world practice and outcomes. Additionally, this is one of the few published studies that investigated that association between IPT initiation/completion and specific ARV regimens. Limitations of this study include the fact that since data was not collected under strict research conditions, the fidelity of all the data points could not be completely assured. For example, IPT completion was marked as yes/no without independent verification using pill counts or other methodology. There was data that was missing for a considerable subset of patients, such as the specific contraindication precluding use of IPT, which would have useful to better describe the program results. Additionally, there was no longitudinal information available on long-term follow-up or patient outcomes which would have allowed for a more thorough analysis of programmatic impact.

Furthermore, as an observational study, we are unable to infer an outright causal link between the independent variables and the outcomes. For example, in Botswana, one reason for the prescribing of different ARV regimens (such as moving from a 1st line therapy to an alternative therapy) is due to the appearance of clinical toxicity, often renal or hepatic, with certain medications.[23] A patient's propensity to develop such side effects from ART may be associated with the initiation or completion of IPT as opposed to an interaction between isoniazid and the specific ARV itself. There were few demographic or clinical variables available for analysis, such as socioeconomic status, CD4 count, or clinical co-morbidities, which may have accounted for some of the variation in outcome measures and also may have been associated with the predictor variables, representing unmeasured residual confounding. Lastly, overall daily pill burden was unmeasured and was extrapolated from the daily ARV pill count; actual overall daily pill burden could also be related to coexisting medical conditions would may influence the choice of ARV

regimen (as well as indicate patient's overall state of health), which could conceivably be related to IPT initiation and completion.

IPT completion rates among those who started IPT in this cohort of PLHIV were high and offer encouragement to program managers implementing IPT programs in similar settings. However, IPT initiation rates could be further improved, particularly in males and pregnant females, whom may benefit from targeted educational interventions. We have also shown that specific ARV regimens can be related to both IPT completion as well as IPT initiation and should be considered when counseling individual patients and setting programmatic expectations; a portion of this relationship is possibly secondary to the various pill burdens associated with different ARV regimens, as well as side effects that may result from the combination with isoniazid. Addressing these factors is essential to the continuation of successful IPT programs in PLHIV as framed within the global pursuit to meet national, WHO, and United Nations goals of curtailing TB transmission worldwide.

Tables and Figures:

Figure 1: TPT Patient Screening and Treatment Algorithm

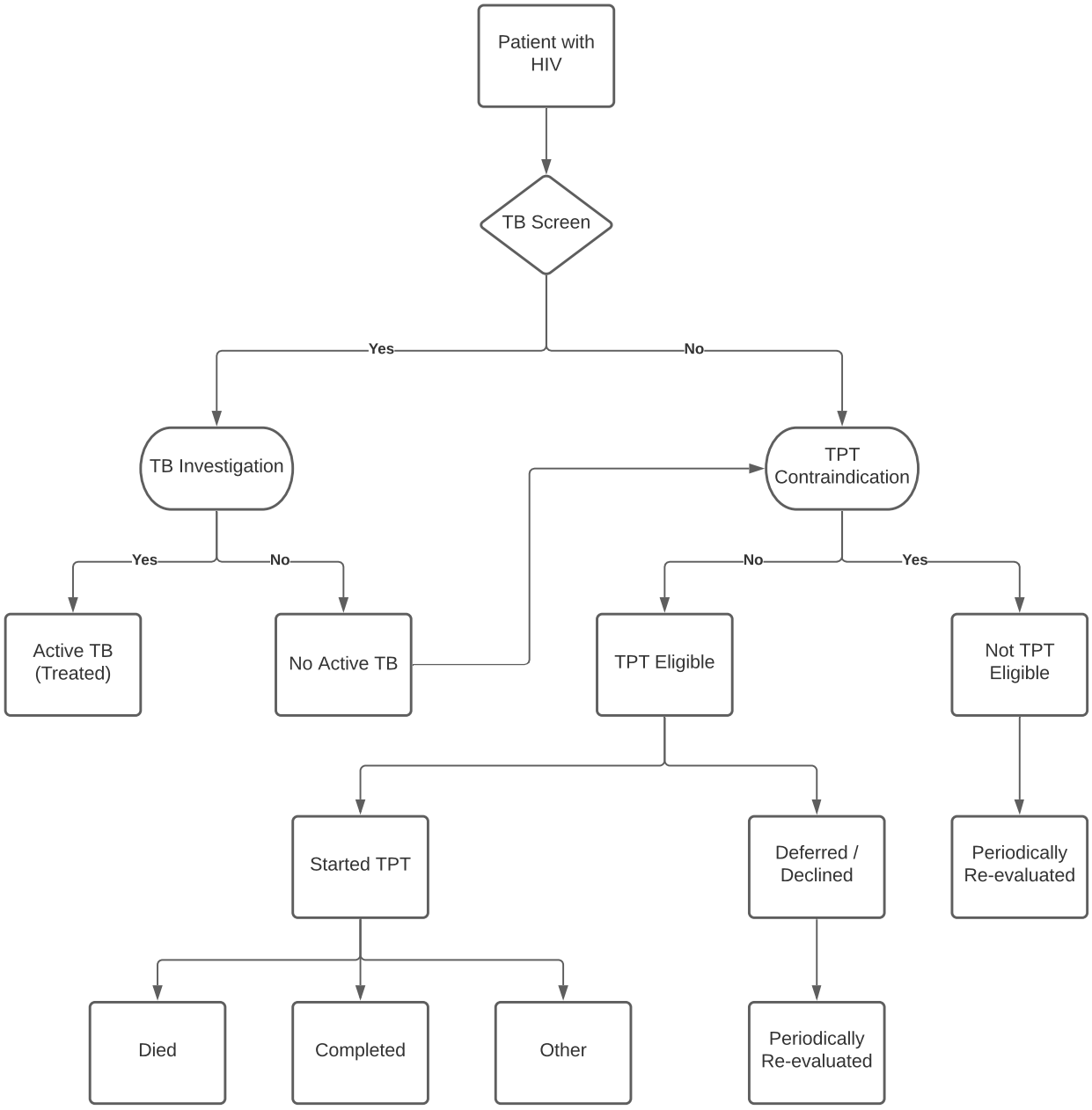

Figure 2: TPT Study Patient Flow

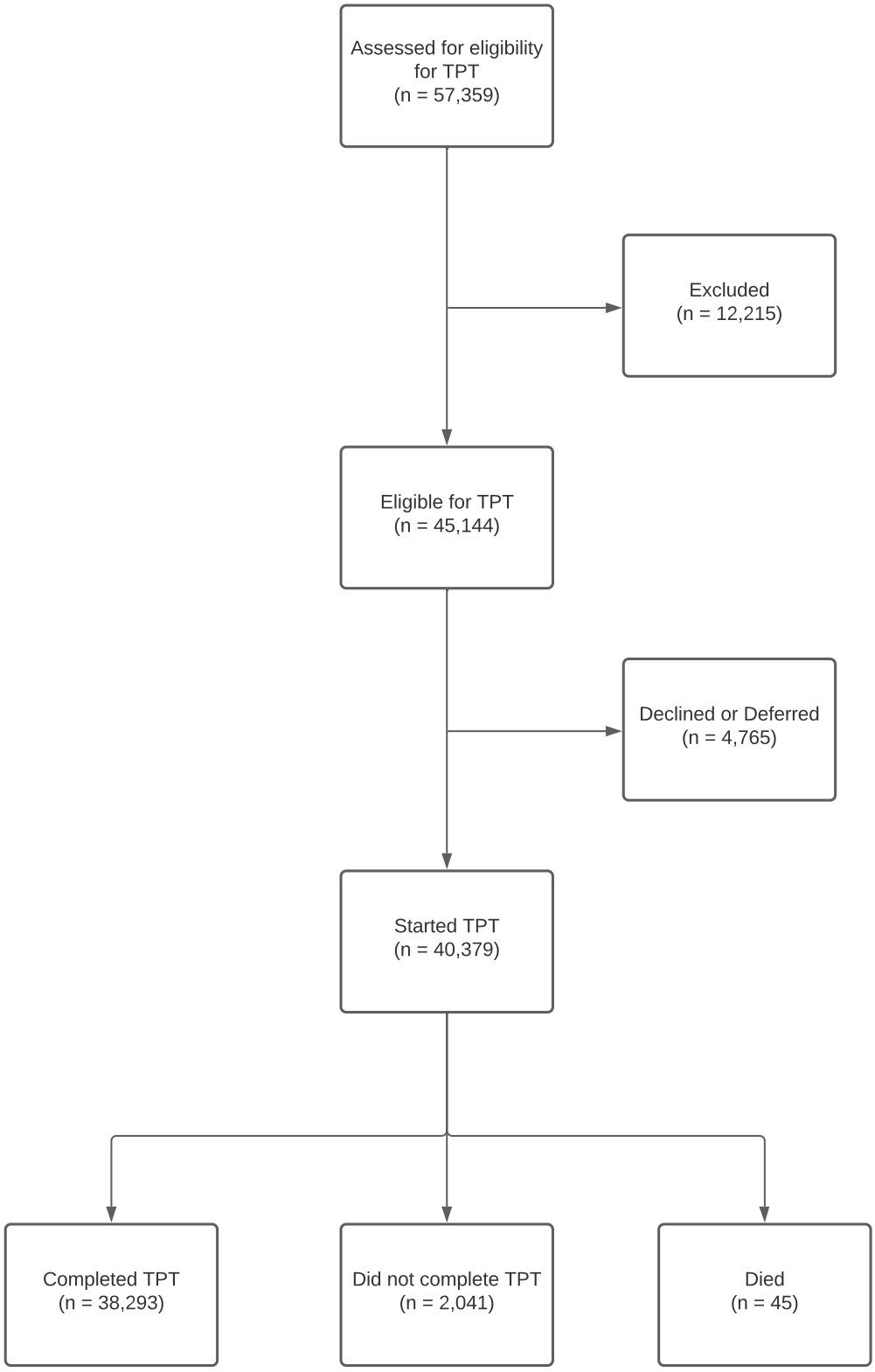

Figure 3: Distribution of Contraindications

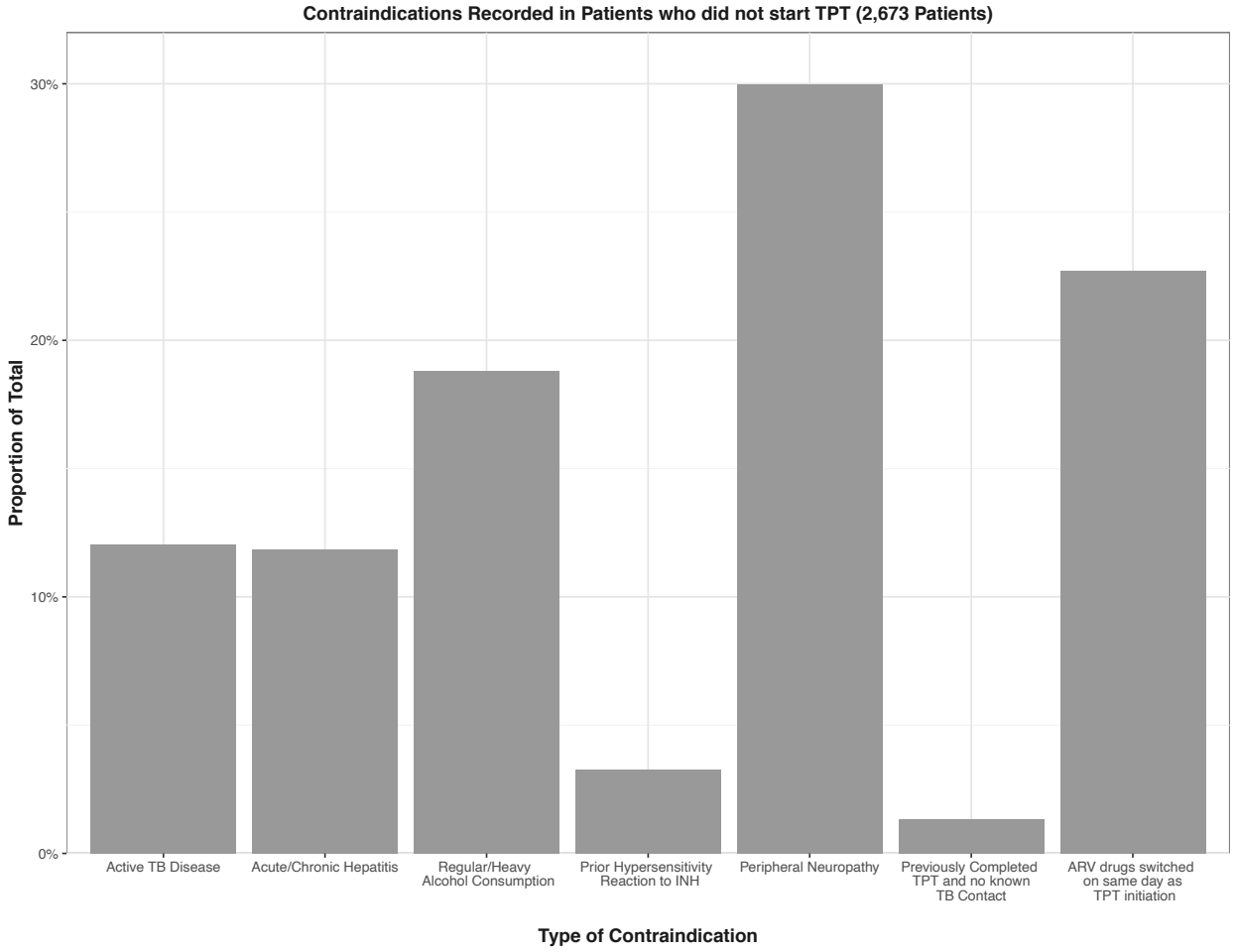

Figure 4: Distribution of Deferrals

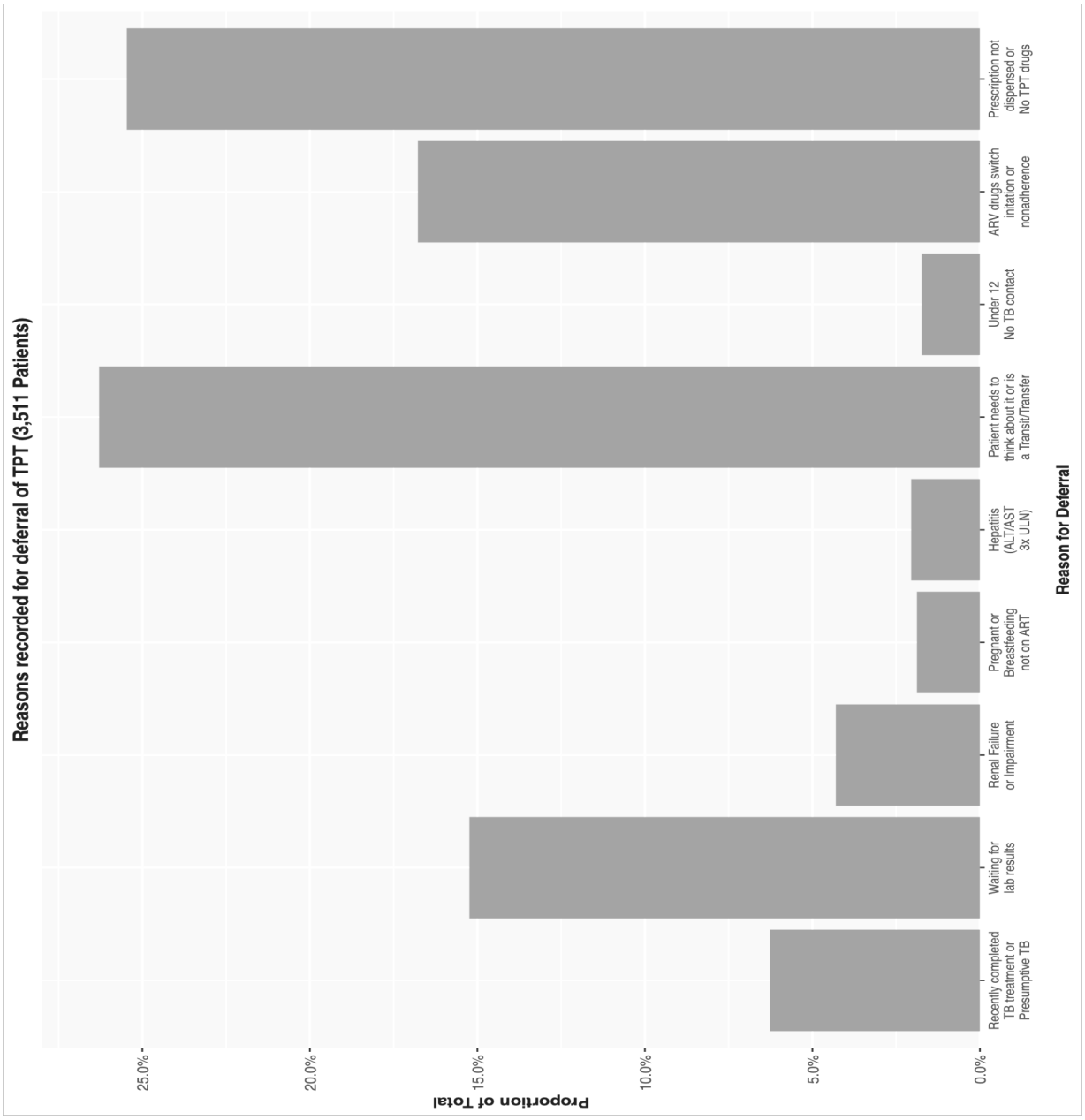

Table 1: Patient Characteristics by TPT Initiation Status

Table 1: Patient Characteristics by TPT Initiation Status			
	TPT Initiated (N = 40,379)	**TPT Not Initiated (N = 16,980)**	**Overall (N = 57,359)**
Age in years (Mean (SD))	43.5 (11.6)	42.6 (12.8)	43.2 (11.9)
Gender (%)			
Female	26,265 (65.0)	10,339 (60.9)	36,604 (63.8)
Male	14,114 (35.0)	6,641 (39.1)	20,755 (36.2)
Pregnacy (% among females)			
Not Pregnant	25,806 (98.2)	9,950 (96.2)	35,756 (97.7)
Pregnant	459 (1.8)	389 (3.8)	848 (2.3)
District (%)			
District 15	14,863 (36.8)	11,621 (68.4)	26,484 (46.2)
District 16	8,903 (22.0)	2,520 (14.8)	11,423 (19.9)
District 3	4,873 (12.1)	258 (1.5)	5,131 (8.9)
District 9	3,787 (9.4)	719 (4.2)	4,506 (7.9)
District 5	3,583 (8.9)	472 (2.8)	4,055 (7.1)
District 17	2,450 (6.1)	838 (4.9)	3,288 (5.7)
District 6	1,654 (4.1)	412 (2.4)	2,066 (3.6)
Other District	266 (0.7)	140 (0.8)	406 (0.7)
ARV Regimen (%)			
TDF/FTC/EFV	11,671 (34.7)	3,722 (32.9)	15,393 (34.2)
TDF/3TC/DTG	11,668 (34.7)	3,381 (29.9)	15,049 (33.5)
AZT/3TC_EFV	3,021 (9.0)	1,205 (10.6)	4,226 (9.4)
AZT/3TC_NVP	3,003 (8.9)	1,119 (9.9)	4,122 (9.2)
TDF/FTC_NVP	1,977 (5.9)	827 (7.3)	2,804 (6.2)
ABC/3TC/DTG + TAF/ED	921 (2.7)	224 (2.0)	1,145 (2.5)
TDF/FTC_LPV/R	594 (1.8)	347 (3.1)	941 (2.1)
Other	789 (2.3)	495 (4.4)	1,284 (2.9)
Daily ARV Pill Count (%)			
1	23,339 (71.0)	7,103 (65.6)	30,442 (69.7)
2	2,898 (8.8)	1,051 (9.7)	3,949 (9.0)
3	6,618 (20.1)	2,671 (24.7)	9,289 (21.3)

Table 2: Odds Ratios and Confidence Intervals for IPT Completion

Table 2: Odds Ratios and 95% Confidence Intervals for IPT Completion among those patients who initiated IPT according to Age; Gender; ARV Regimen; Pregnancy Status; and Daily Pill Count.

	Crude Proportion of IPT Completion	Unadjusted Model		Fully Adjusted Model+		Fully Adjusted Model#		Fully Adjusted Model^	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age in years (Mean (SD))	N/A	0.988*	(0.984, 0.992)	0.999	(0.994, 1.004)	1.000	(0.994, 1.006)	0.997	(0.993, 1.002)
Gender									
Female	94.8%	Referent	Referent	Referent	Referent			Referent	Referent
Male	94.8%	0.982	(0.888, 1.086)	1.047	(0.93, 1.181)			1.047	(0.903, 1.139)
ARV Regimen									
TDF/FTC/EFV	95.4%	Referent	Referent	Referent	Referent	Referent	Referent		
TDF/3TC/DTG	95.9%	1.210*	(1.055, 1.388)	1.243*	(1.078, 1.434)	1.307*	(1.093, 1.564)		
AZT/3TC_EFV	92.8%	0.612*	(0.516, 0.730)	0.747*	(0.621, 0.903)	0.587*	(0.449, 0.776)		
AZT/3TC_NVP	93.8%	0.712*	(0.595, 0.856)	0.824	(0.680, 1.002)	0.819	(0.662, 1.018)		
TDF/FTC_NVP	94.9%	0.895	(0.713, 1.136)	0.980	(0.770, 1.259)	0.919	(0.711, 1.200)		
ABC/3TC/DTG + TAF/ED	91.9%	0.564*	(0.433, 0.746)	0.816	(0.616, 1.096)	0.817	(0.566, 1.210)		
TDF/FTC_LPV/R	91.8%	0.487*	(0.360, 0.673)	0.700*	(0.509, 0.983)	0.872	(0.582, 1.354)		
Other	92.1%	0.623*	(0.464, 0.853)	0.952	(0.703, 1.317)	0.854	(0.599, 1.250)		
Pregnancy Status									
Not Pregnant	95.7%	Referent	Referent			Referent	Referent		
Pregnant	92.6%	0.705	(0.485, 1.070)			0.905	(0.591, 1.457)		
Daily ARV Pill Count									
1	95.6%	Referent	Referent					Referent	Referent
2	93.9%	0.691*	(0.580, 0.828)					0.824*	(0.685, 0.997)
3	93.1%	0.583*	(0.517, 0.659)					0.706*	(0.617, 0.810)

* indicates $p < 0.05$

+Adjusted for Age, Gender, ARV Regimen, and Treating Clinic

#Adjusted for Age, ARV Regimen, Pregnancy Status, and Treating Clinic

^Adjusted for Age, Gender, Pill Burden, and Treating Clinic

Table 3: Odds Ratios and Confidence Intervals for IPT Initiation

Table 3: Odds Ratios and 95% Confidence Intervals for IPT Initiation among all study patients according to Age; Gender; ARV Regimen; and Daily Pill Count.

	Crude Proportion of TPT Initiation	Unadjusted Model		Fully Adjusted Model+		Fully Adjusted Model^	
		OR	95% CI	OR	95% CI	OR	95% CI
Age in years (Mean (SD))	N/A	1.006*	(1.004, 1.007)	1.005*	(1.003, 1.007)	1.004*	(1.002, 1.006)
Gender							
Female	71.8%	Referent	Referent	Referent	Referent	Referent	Referent
Male	68.0%	0.837*	(0.806, 0.868)	0.794*	(0.755, 0.835)	0.799*	(0.76, 0.84)
ARV Regimen							
TDF/FTC/EFV	75.8%	Referent	Referent	Referent	Referent		
TDF/3TC/DTG	77.5%	1.101*	(1.044, 1.161)	1.034	(0.975, 1.096)		
AZT/3TC_EFV	71.5%	0.800*	(0.741, 0.863)	0.761*	(0.698, 0.830)		
AZT/3TC_NVP	72.9%	0.856*	(0.792, 0.926)	0.761*	(0.698, 0.831)		
TDF/FTC_NVP	70.5%	0.762*	(0.698, 0.834)	0.711*	(0.645, 0.785)		
ABC/3TC/DTG + TAF/ED	80.4%	1.311*	(1.130, 1.528)	0.794*	(0.671, 0.943)		
TDF/FTC_LPV/R	63.1%	0.546*	(0.476, 0.627)	0.670*	(0.578, 0.778)		
Other	61.5%	0.508*	(0.452, 0.572)	0.531*	(0.467, 0.605)		
Pregnancy Status							
Not Pregnant	72.2%	Referent	Referent				
Pregnant	54.1%	0.455*	(0.397, 0.522)				
Daily ARV Pill Count							
1	76.7%	Referent	Referent			Referent	Referent
2	73.4%	0.752*	(0.691, 0.819)			0.721*	(0.662, 0.784)
3	71.3%	0.752*	(0.704, 0.804)			0.743*	(0.700, 0.790)

* indicates $p < 0.05$

+Adjusted for Age, Gender, ARV Regimen, and Treating Clinic

#Adjusted for Age, ARV Regimen, Pregnancy Status, and Treating Clinic

^Adjusted for Age, Gender, Pill Burden, and Treating Clinic

Table 4: Odds Ratios and Confidence Intervals for Death on IPT

Table 4: Odds Ratios and 95% Confidence Intervals for Death among those who initiated IPT according to Age; Gender; ARV Regimen; and Daily Pill Count.

	Crude Proportion of Death	Unadjusted Model		Fully Adjusted Model+		Fully Adjusted Model^	
		OR	95% CI	OR	95% CI	OR	95% CI
Age in years (Mean (SD))	N/A	1.046*	(1.021, 1.071)	1.061*	(1.027, 1.095)	1.051*	(1.019, 1.084)
Gender							
Female	0.10%	Referent	Referent	Referent	Referent	Referent	Referent
Male	0.13%	1.24	(0.672, 2.236)	0.889	(0.400, 1.885)	0.840	(0.384, 1.743)
ARV Regimen							
TDF/FTC/EFV	0.09%	Referent	Referent	Referent	Referent		
TDF/3TC/DTG	0.08%	0.902	(0.358, 2.238)	1.028	(0.399, 2.619)		
AZT/3TC_EFV	0.13%	1.550	(0.425, 4.637)	0.956	(0.251, 3.055)		
AZT/3TC_NVP	0.10%	1.166	(0.261, 3.815)	1.229	(0.265, 4.307)		
TDF/FTC_NVP	0.10%	1.181	(0.181, 4.484)	1.468	(0.217, 6.038)		
ABC/3TC/DTG + TAF/ED	0.00%	0.000	(0.00, 5.6E+7)	0.000	(0.0, 1.6E+43)		
TDF/FTC_LPV/R	0.51%	5.901*	(1.320, 19.35)	6.383*	(1.323, 23.31)		
Other	0.13%	1.495	(0.081, 7.819)	1.178	(0.063, 6.361)		
Daily ARV Pill Count							
1	0.08%	Referent	Referent			Referent	Referent
2	0.07%	0.849	(0.135, 2.924)			0.637	(0.100, 2.261)
3	0.15%	1.857	(0.829, 3.913)			1.404	(0.584, 3.243)

* indicates $p < 0.05$

+Adjusted for Age, Gender, ARV Regimen, and Treating Clinic

^Adjusted for Age, Gender, Pill Burden, and Treating Clinic

Table 5: Odds Ratios and Confidence Intervals for Side Effects leading to IPT discontinuation

Table 5: Odds Ratios and 95% Confidence Intervals for Side Effects leading to discontinuation of IPT among those patients that initiated IPT according to Age; Gender; ARV Regimen; Pregnancy Status; and Daily Pill Count.

	Crude Proportion of Side Effects	Unadjusted Model		Fully Adjusted Model+		Fully Adjusted Model#		Fully Adjusted Model^	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age in years (Mean (SD))	N/A	1.031*	(1.024, 1.037)	1.017*	(1.009, 1.025)	1.014*	(1.004, 1.024)	1.019*	(1.011, 1.027)
Gender									
Female	1.77%	Referent	Referent	Referent	Referent			Referent	Referent
Male	1.62%	0.915	(0.779, 1.072)	0.836	(0.690, 1.009)			0.849	(0.706, 1.018)
ARV Regimen									
TDF/FTC/EFV	1.41%	Referent	Referent	Referent	Referent	Referent	Referent		
TDF/3TC/DTG	1.03%	0.730*	(0.575, 0.925)	0.805	(0.630, 1.026)	0.854	(0.630, 1.156)		
AZT/3TC_EFV	3.31%	2.408*	(1.867, 3.092)	1.666*	(1.263, 2.188)	2.272*	(1.530, 3.330)		
AZT/3TC_NVP	3.06%	2.218*	(1.707, 2.865)	1.675*	(1.268, 2.202)	1.804*	(1.319, 2.463)		
TDF/FTC_NVP	2.12%	1.523*	(1.069, 2.123)	1.144	(0.788, 1.628)	1.257	(0.843, 1.845)		
ABC/3TC/DTG + TAF/ED	2.82%	2.052*	(1.320, 3.064)	1.619*	(1.023, 2.469)	2.179*	(1.237, 3.648)		
TDF/FTC_LPV/R	3.87%	2.817*	(1.762, 4.302)	1.506	(0.922, 2.360)	1.422	(0.768, 2.468)		
Other	2.53%	1.844*	(1.118, 2.877)	1.020	(0.612, 1.613)	1.108	(0.595, 1.917)		
Pregnancy Status									
Not Pregnant	1.73%	Referent	Referent			Referent	Referent		
Pregnant	3.92%	2.332*	(1.392, 3.660)			1.712	(0.951, 2.862)		
Daily ARV Pill Count									
1	0.93%	Referent	Referent					Referent	Referent
2	1.72%	1.953*	(1.484, 2.536)					1.417*	(1.061, 1.868)
3	2.31%	2.726*	(2.277, 3.260)					1.790*	(1.463, 2.189)

* indicates $p < 0.05$

+Adjusted for Age, Gender, ARV Regimen, and Treating Clinic

#Adjusted for Age, ARV Regimen, Pregnancy Status, and Treating Clinic

^Adjusted for Age, Gender, Pill Burden, and Treating Clinic

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