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Research Article

Predictors of Isoniazid Preventive Therapy Discontinuation among People Living With HIV Attending Care and Treatment: Analysis of 2013-2017 Routine HIV Data Tanzania

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Abstract

Background: Tuberculosis disease is a common opportunistic infection in people living with HIV not initiated Isoniazid Preventive Therapy dose. In 2015 WHO recommended at least, 36-months course for significant population benefits towards reducing Tuberculosis infections in the high-risk population, although the minimum recommended is six months dose. Six months dose completion is sub-optimal and enrolled clients in the treatment discontinue within three months following initiation. The time interval after three months following initiation clients have low dose discontinuation. Isoniazid Preventive Therapy discontinuation within three months following initiation is high although is inadequately routine documented at health facility settings in Tanzania. The study determined predictors of Isoniazid Preventive Therapy discontinuation within three months following initiation among People Living with HIV aged 15 and above years in Dar es Salaam region.

Methods: A retrospective cohort study was conducted using secondary data which are routinely collected. Researcher abstracted data from 58 care and treatment clinics in the region. The study recruited clients who screened negative for TB symptoms and initiated IPT from January 2013 to June 2017. Multilevel Modified Poisson regression model with robust standard errors were used to estimate Prevalence Ratios (PR), 95% Confidence Interval (CI) and p-values at 5% significance level for predictors of IPT discontinuation within three months following initiation among HIV infected individuals. Health facility cluster adjusted model was used to estimate the random effects. The covariates that were adjusted in the final model are age, sex, years of Isoniazid Preventive Therapy, health facility ownership, ART status, WHO stage, CD4+ cells/μL and functional status.

Results: A total of 29,382 clients were initiated Isoniazid Preventive Therapy, with 21,808 (74%) female. Overall 11,826 (40.3%) discontinued IPT, decreasing from 57.2% (1,062/1,857) in year 2013 to 22.9% (883/3,856) in year 2017. Adjusted findings and show that clients with CD4+ cells/μL between 100 to 349 +cells/μL had significant higher Isoniazid Preventive Therapy, discontinuation prevalence than those with CD4+ <100 + cells/μL (APR: 1.06: 95%CI: 1.03-1.09; *P*-value <0.001). Patients not on ART had significant higher Isoniazid Preventive Therapy, discontinuation prevalence than those on ART (APR: 1.47: 95%CI: 1.31-1.66; *P*-value <0.001). Significantly higher IPT discontinuation in age category 25-34 and 35-44 years (APR: 1.09; 95%CI: 1.04-1.16; *P*-value: 0.001)and (APR: 1.04:95%CI: 1.02-1.07; *P*-value <0.001) than those aged greater or equal to 45years. There was significant lower IPT discontinuation within three months following initiation in year 2016 (APR: 0.79:95%CI: 0.63-0.98; *P*-value: 0.03) and 2017 APR: 0.64: 95%CI: 0.48-0.84; *P*-value: 0.001) than in year 2013.

Conclusion: IPT discontinuation is high although was decreasing over time. Significant higher prevalence of IPT discontinuation was seen in PLHIV with CD4+ between 100 to 349 cells/μL. Patients who were not on ART had lower prevalence than baseline group. Therefore, much intervention for reducing IPT discontinuation within three months following initiation in exposed groups are highly needed, although there was decreasing trend as per year increase.

Keywords: IPT discontinuation; HIV; Tuberculosis; Predictors; Tanzania

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Abbreviations

CPR: Crude Prevalence Ratio; APR: Adjusted Prevalence Ratio; ART: Antiretroviral Therapy; CI: Confidence Interval; CTC: Care and Treatment Clinics; RERC: Research and Ethical Review Committee; HIV: Human Immunodeficiency Virus; IPT: Isoniazid Preventive Therapy; IQR: Inter Quartile Range; KCMUCO: Kilimanjaro Christian Medical University College; MOHCDGEC: Ministry of Health, Community Development, Gender Elderly and Children; PLHIV: People Living with HIV; TB: Tuberculosis; WHO: World Health Organization

Background

Tuberculosis disease is common in people living with HIV. TB/HIV burden is 13% worldwide, with over 78% of cases from Africa. This dual infection contributes about 30-40% of all TB deaths. It accounts 10% of TB deaths especially at high endemic regions in Africa [1-7]. Isoniazid is one of the drugs used for first line treatment for TB infection and prevents HIV infected individuals from developing to active TB [6,8]. The life risk of patients not initiated IPT is 20-37 times higher than those exposed to this preventive therapy [5,9-12]. Despite in WHO 2015 recommended at least 36-months course for significant population benefits towards reducing Tuberculosis infections in the high-risk population and endemic areas, but still the crucial minimum recommended IPT dose is six months [6,11]. Previous epidemiological studies evidenced that, at least six months IPT dose completion reduces risks of TB cases by 33-60% in HIV infected people [2,6,13-22].

Moreover, at least six months dose completion is still sub-optimal and literatures revealed dose discontinuation at least six and above months dose ranged from 1%-61% [23-32], and in Tanzania was from 2%-35% [1,20,33-35]. Elsewhere literatures show that many HIV clients discontinue IPT dose within three months following initiation. These previous studies show that after three months following initiation clients have low discontinuation proportions in Zimbabwe, Ethiopia and Malawi (16.6%, 17.7% and 18.6%) respectively [27,36,37]. None of these studies determined discontinuation of IPT dose within three months following initiation at routine settings in Tanzania. IPT discontinuation in the first three months following initiation is highly anticipated and still insufficiently documented at care and treatment routine settings in Tanzania. IPT discontinuation burden leads to high remained risk of acquiring TB disease, mortality, morbidity, more treatment costs in patients and failure in achieving Tanzania's incidences targets [1,2,38,39]. The study determined predictors of IPT discontinuation in the first three months following initiation in PLHIV aged greater or equal to 15 years in Dar es Salaam region. IPT discontinuation information within three months following initiation will be useful to the Ministry of Health, Community Development, Gender, Elderly and Children to plan better interventions for reducing dose discontinuation towards preventing TB cases in HIV positive people [20,33,40-43].

Methods

A retrospective cohort study using secondary analysis of de-identified routinely collected data of PLHIV attending HIV services in 58 Care and Treatment Clinics (CTC) in Dar es Salaam region was conducted. The study retrieved data from the electronic database, which is used for all routine clinic visits by PLHIV. The national TB/HIV and HIV guidelines recommend that all PLHIV should be screened for TB at every clinic visit using standard TB screening tools [4]. All PLHIV aged 15 years or more who screened negative TB and were initiated IPT between January 2013 and June 2017 were eligible in the analysis. (Figure 1) shows the total clients enrolled in HIV care, and the exclusion for different reasons (Figure 1).

Study Variables

All subsequent clinic records of those who initiated IPT were reviewed for adherence to IPT at their scheduled monthly visits.

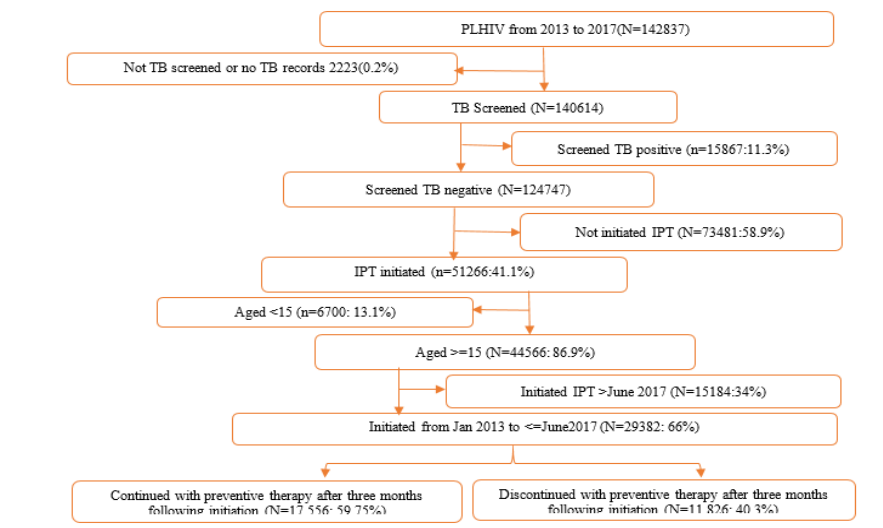

Figure 1 Flow chart determining how participants were selected.

The outcome variable is IPT discontinuation that was defined as the failure to collect IPT drugs within three months following initiation. This either is due to lost to follow up, death, TB infection or stopped because of any reasons. The independent variables were sex, age, functional status, pregnancy status, marital status, ART status, WHO clinical stage and CD4+ cells/μLat IPT initiation. Records of all patients who initiated IPT in Care and Treatment Health Facilities (CTC) in Dar es Salaam region from January in year 2013 to June 2017. All these study variables were secondary retrieved and abstracted from the CTC2 databases.

Data Analysis

Data analysis was performed using STATA Corp, College station, TX version 15.0 . Continuous variables such as age and CD4+ cells/μLwere transformed to categorical variables. Descriptive statistics that were used are frequency and proportion for category variables. The chi-square test was used to compare the differences of IPT discontinuation proportions across general and clinical patient characteristics. A multilevel modified Poisson regression model was used to determine the Prevalence Ratio (PR) and 95% confidence interval (95%CI) of factors associated with IPT discontinuation. Multilevel modelling was used to estimate the predictors of IPT discontinuation, while accounting for the dependency of individuals within health facilities. Intra Class Correlation (ICC) was used to measure the proportion of variability due to health facilities level. The process of building this regression started from simple to complex model. The final model was built after adjusting variables which were statistically significant at univariate analysis.

Ethics

Ethics approval for the study was obtained from the Kilimanjaro Christian Medical University college - Research and Ethical Review Committee in 2018 (KCMUCo-RERC approval number 2388). Secondary use of the data from the electronic database was requested and approved by National Aids, Sexual Transmitted Infections (STIs) and Hepatitis Control Program (NASHCoP), which owns the data on behalf of Ministry of Health. Patient consent was not required for this routine data analysis.

Results

A total of 142,837 PLHIV were registered in CTC in Dar-es-Salaam in the study period. Of these 2,223 (0.2%) had no record of TB screening. Of 140,614 patients, 124,747 (88.7%) had record of a negative TB screening results. Of those who screened negative 51,266 (41%) initiated IPT and 13.1% of these aged less

Table 1: Demographic and Clinical characteristics of 29,382 Participants Attended HIV Services from 2013 to 2017 in Dares Salaam.

Variable	Baseline Characteristics of Clients n(%)	Characteristics of Clients at Discontinuation Status n(%)	Clients who Discontinued IPT within Three Months Following Initiation (n = 11, 826: 40.3%)	*P*-value
Age Category				
15-24	1,569 (5.34)	1,454 (4.95)	606 (41.68)	0.166
25-34	5,546 (18.88)	5,216 (17.75)	2,118 (40.61)	
35-44	11,845 (40.31)	11,708 (39.85)	4,759 (40.65)	
≥ 45	10,422 (35.47)	11,004 (37.45)	4,343 (39.47)	
Sex				
Male	21,808 (74.22)	21,808 (74.22)	8,733 (40.04)	0.226
Female	7,574 (25.78)	7,574 (25.78)	3,093 (40.84)	
Marital Status				
Single	7, 825 (30.33)	7,847 (30.31)	5,237 (39.08)	<0.001
Married/cohabiting	13,368 (51.82)	13,401 (51.77)	3,313 (42.22)	
Divorced/widowed	4, 605 (17.85)	4,640 (17.92)	1,741 (37.52)	
Year of IPT Initiation				
2013	1,857 (6.32)	1,857 (6.32)	1,06 2 (57.19)	<0.001
2014	5,169 (17.59)	5,169 (17.59)	2,824 (54.63)	
2015	7,754 (26.39)	7,754 (26.39)	3,812 (49.16)	
2016	10,746 (36.57)	10,746 (36.57)	3,245 (30.20)	
2017	3,856 (13.12)	3,856 (13.12)	883 (22.90)	
PLHIV by Health Facility Ownership				
Public	20,538 (69.90)	20,272 (68.99)	9,244 (45.60)	<0.001
Private	8,844 (30.10)	9,110 (31.01)	2,582 (28.34)	
ART Status				

Not on ART	826 (2.81)	515 (1.75)	367 (71.26)	<0.001
On ART	28,539 (97.19)	28,859 (98.25)	11,451 (39.68)	
WHO Clinical Stage				
I	5,219 (17.97)	5,026 (17.26)	1,790 (35.61)	<0.001
II	6,932 (23.87)	6,758 (23.21)	2,616 (38.71)	
III	14,549 (50.11)	14,910 (51.20)	6,192 (41.53)	
IV	2,335 (8.04)	2,427 (8.33)	1,050 (43.26)	
CD4+ cells/μL				
< 100	13,717 (46.80)	13,687 (46.79)	5,437 (39.72)	< 0.001
100-349	9,935 (33.90)	9,927 (33.94)	3,784 (38.12)	
≥ 350	5,657 (19.30)	5,635 (19.27)	2,550 (45.25)	
Functional Status				
Work	29,118 (99.17)	29,032 (99.11)	11,696 (40.29)	< 0.001
Ambulatory	27 (0.09)	34 (0.12)	22 (64.71)	
Bedridden	217 (0.74)	227 (0.77)	75 (33.04)	
Co-Medications				
Cotrimoxazole	8,400 (71.26)	7,180 (71.46)	2,885 (40.18)	0.002
Fluconazole	42 (0.36)	22 (0.22)	12 (54.55)	
Others	3,346 (28.38)	2,845 (28.32)	1,045 (36.73)	
Visit Type				
Scheduled	27,231 (92.76)	26,512 (90.32)	10,668 (40.24)	0.013
Traced back after LTFU	150 (0.51)	238 (0.81)	73 (30.67)	
Treatment supported drugs pick up	112 (0.38)	287 (0.98)	111 (38.68)	
Unscheduled	1,864 (6.35)	2, 317 (7.89)	960 (41.43)	

than 15 years were excluded. Participants 29,382 were included in the study. The demographic and clinical characteristics of the 29,382 participants who initiated IPT are shown in (Table 1) with 21,808 (74.2%) female, the dominant age category was 35- 44 years with 11,845 (40.31%) and 11,708 (39.9%) at baseline and discontinuation status respectively (Table 1). Majority 28,859 (98.3%) clients were on ART at discontinuation status, of these 11, 451 (39.7%) discontinued IPT within three months following initiation. Majority 13,717 (46.80) clients at initiation had CD4+ less 100 cells/μL similarly to 13, 687 (46.79%) at discontinuation status. Patients who were initiated IPT with greater or equal CD4+ 350 cells/μL are 5,657 (19.30%) and at discontinuation status 5, 635 (19.3%) clients were in this CD4+ cells/μL category. Many 2, 550 (45.3%) of clients discontinued IPT with CD4+ greater or equal to 350 cells/μL (Table 1).

Isoniazid Preventive Therapy Discontinuation

From January, year2013 to December 2017, the IPT discontinuation within the three months following initiation was 40.3% , but the IPT discontinuation within three months following initiation decreased from 57.2% in year 2013 to 22.9% in 2017 (Figure 2). There was high proportion of IPT discontinuation in the second month following initiation.

Predictors Isoniazid Preventive Therapy Discontinuation within Three Months Following Initiation

Univariate analysis accounting health facility random effects indicates there was 58% higher IPT discontinuation among those who were not on ART (PR: 1.58: 95%CI: 1.37-1.81). Clients with 25 to 34 and 35 to 44 years old had 9% and 4% higher IPT discontinuation as compared to patients with greater or equal to 45 years old (PR:1.09: 95%CI: 1.02-1.17) and (PR:1.04: 95%CI: 1.02-1.07) respectively. Patients with CD4+ 100 to349 cells/μL and greater or equal to CD4+ 350 cells/μL had higher IPT discontinuation (PR: 1.07: 95%CI: 1.04-1.10) and (PR: 1.09: 95%CI: 1.03-1.15) respectively. As years increase there was statistically significant lower IPT discontinuation, such as in year 2016 and 2017 (PR: 0.78: 95%CI: 0.63-0.98) and (PR: 0.63: 95%CI: 0.48-0.83) respectively.

Multivariate multilevel modified Poisson analysis shows results of complex model after adjusting for other factors and accounting the random effects of health facility. The adjusted PR showed that male had 2% insignificant higher prevalence of discontinuing IPT within three months following initiation. The patients not on ART had a 47% higher IPT discontinuation than those not on ART (PR: 1.47: 95%CI: 1.31-1.66).Clients with CD4+ from 100 to349 cells/μL had 6% higher of IPT discontinuation as compared to those with less than CD4+ 100 cells/μL (PR: 1.06: 95%CI: 1.03-1.09). Similarly, patients with CD4+ greater or

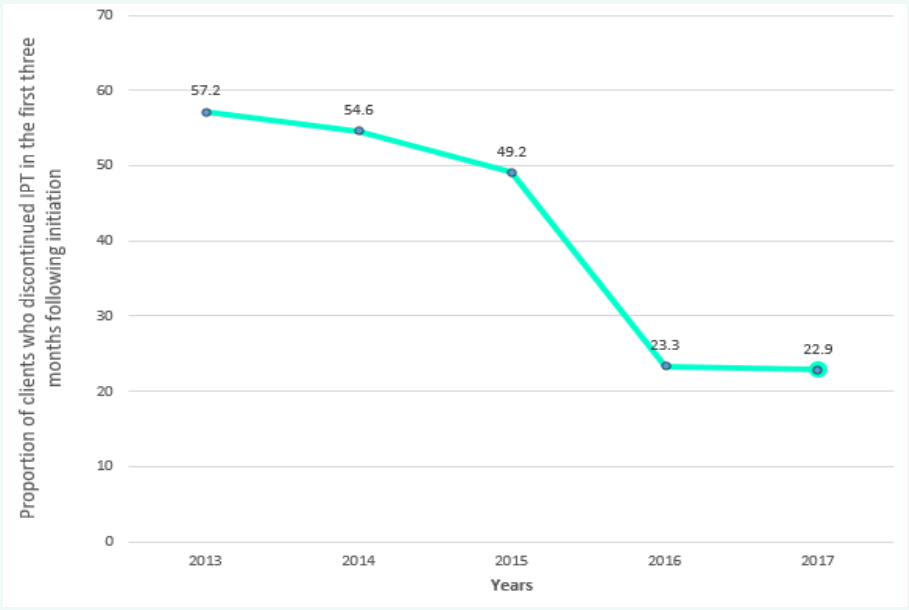

Figure 2 Overall trend of IPT discontinuation in the first three months following initiation by years.

equal to 350 cells/μL had 6% higher of IPT discontinuation as compared to those with less than 100 cells/μL (PR: 1.06: 95%CI: 1.02-1.11). As year increase there is statistically significant decreased chance of IPT discontinuation in year 2017 (PR: 0.64: 95%CI: 0.48-0.84) as compared to year 2013 Results show that Intra-Class Correlation (ICC) was 0.066. This means percentage of variability caused by sum square between health facilities was 6.6 % (Table 2).

Discussion

These findings show that IPT discontinuation within three months following initiation among PLHIV attending routine HIV care services in Dar es Salaam, Tanzania. The findings showed female were almost 74% more versus 26% male in the IPT program. This may be due to health seeking behaviours and retention differ between male and female. The overall IPT discontinuation proportion was 40.3% and it decreased over the four years from 57.2% in year 2013 to 22.9% in year 2017. This probably reflects the improved HIV services provided in the health facilities in Tanzania [44]. This is consistent with the improvements of TB/HIV services in Tanzania, which showed increased HIV testing services, ART initiation, HIV services, TB screening and accessibility of health facility [44]. There was high IPT discontinuation in the first three months which was high as compared studies in Malawi (18.6%), Zimbabwe (16.6%) and Ethiopia (17.6%) [27,36,37]. Patients may be discouraged by the long treatment duration of IPT and the need to attend clinic every month [27,36,37]. A number of interventions such as automated mobile phone Short Message Services (SMS), smart-phone applications and home visits by lay counsellors maybe considered to help patients initiated IPT to retain in the treatment services as were recommended in the retrospective cohort study from Malawi [37]. Interventions for further improve retention health care providers may extensively educate patients immediately after HI diagnosis and support more the immunosuppressed patients as well as providing literacy on the benefits of IPT [37]. Health facilities may also focus on supporting patients to complete their first, second and third months of IPT initiation as most patients drop out at these stages [37].

The findings showed that IPT discontinuation within three months following initiation was insignificant by sex of patients; male patients had higher chance as compared to female. This can be explained that health seeking behaviour differ between male and female PLHIV at routine settings. Patients with high CD4+ greater or equal 350 cells/μL had higher prevalence of IPT discontinuation in the first three months following initiation, which is inconsistent with findings from Kenya and Brazil [25,32]. Possibly patients with high CD4+ cells/μL perceive themselves healthy not at risk of progressing to active TB, and so they do not have seriousness of taking IPT for the full six months. There was statistically significant higher prevalence of IPT discontinuation among clients not ART consistently in Kenya, Zimbabwe and Brazil [25,27,32]. These results indicate that patients who are linked and receive ART services have decreased chances of IPT discontinuation, similarly with study which was conducted in Malawi [37]. Patients who were having age of 25-34 years had higher chance of IPT discontinuation within three months following initiation than 45 and above years. This was consistent to study conducted in Malawi which found that as age becomes large has decreased chance of discontinuation [37].

Strenghs and Limitations of the Study

The study had large sample size which is directly to high power of the study (≥ 90%) to detect the true estimated effects ofrisks factors on IPT discontinuation (Table 3). The study used routinely collected data, which reflected the real practices

Table 2: Determinants of discontinuation with IPT in the first three months following initiation among PLHIV adjust for clustering at health facilities.

Variable	CPR (95%CI)	ICC	P-value	APR (95%CI)	P-value	ICC
Age Category						
15-24	1.02 (0.82-1.27)	9.30%	0.832	1.07 (0.88-1.29)	0.51	
25-34	1.09 (1.02-1.17)		0.01	1.09 (1.04-1.16)	0.001	
35-44	1.04 (1.02-1.07)		0.002	1.04 (1.02-1.07)	< 0.001	
≥ 45	Reference			Reference		
Sex						
Female	Reference	9.30%		Reference		
Male	0.99 (0.96-1.04)		0.995	1.02 (0.98-1.05)	0.254	
Years of IPT Initiation						
2013	Reference	7.00%		Reference		
2014	1.09 (0.87-1.36)		0.454	1.08 (0.86-1.36)	0.484	
2015	1.07 (0.92-1.25)		0.401	1.07 (0.91-1.24)	0.416	
2016	0.78 (0.63-0.98)		0.033	0.79 (0.63-0.98)	0.03	
2017	0.63 (0.48-0.83)		0.001	0.64 (0.48-0.84)	0.001	
Marital Status						
Married/cohabiting	Reference	9.40%				
Single	1.02 (0.98-1.06)		0.357			
Divorced/widowed	0.99 (0.97-1.03)		0.908			
Health Facility Ownership						
Public	Reference	8.90%		Reference		
Private	0.79 (0.55-1.11)		0.167	0.84 (0.99-1.05)	0.235	
ART Status						
On ART	Reference			Reference		
Not on ART	1.58 (1.37-1.81)	9.10%	< 0.001	1.47 (1.31-1.66)	< 0.001	
WHO Stage						
I	Reference	9.20%		Reference		
II	1.03 (0.96-1.11)		0.448	1.02 (0.96-1.07)	0.565	
III	1.01 (0.95-1.08)		0.738	1.04 (0.98-1.09)	0.158	
IV	1.02 (0.89-1.17)		0.784	1.06 (0.95-1.18)	0.311	
CD4+ cells/µL						
<100	Reference	9.30%		Reference		
100-349	1.07 (1.04-1.10)		<0.001	1.06 (1.03-1.09)	<0.001	
≥350	1.09 (1.03-1.15)		0.001	1.06 (1.02-1.11)	0.007	
Functional Status						
Work	Reference	9.30%		Reference		
Ambulatory	1.34 (1.01-1.80)		0.049	1.32 (0.98-1.36)	0.063	
Bedridden	0.97 (0.75-1.29)		0.832	1.02 (0.81-1.29)	0.846	
Visit Type						
Scheduled	Reference	9.30%				6.60%
Traced back after LTFU	0.87 (0.57-1.33)		0.523			
Treatment supported drugs pick up	0.97 (0.83-1.14)		0.722			
Unscheduled	1.06 (0.96-1.17)		0.253			

Key: CPR: Crude Prevalence Ratio; CI; Confidence Interval; APR: Adjusted Prevalence Ratio; ICC: Intra Cluster Correlation.

in Dar es Salaam, and the same analysis can be incorporated into regular analyses of the CTC2 data across Tanzania. The study included longer time interval which helped to account for population dynamicity since IPT program was rollout. The study used multilevel modified Poisson regression, with robust standard errors since the outcome was common, avoiding high posisibility of differential bais and to account for overdispersion. The study accounted for the effects of health facilities by using random effects to adjust for the clustering in the health facility. One limitation was the incomplete and missing data which might underestimated or overestimated the prevalence ratios. Another limitation is that the routinely collected data are collected for patient mangaement and programatic purposes and so some important variables like INH adverse effects for research are not collected.

Conclusion and Recommendations

IPT discontinuation in Dar es Salaam region was high in year 2013 to 2015, at last decreased gradually towards 2017, perhaps is due to general improvement in HIV care services in Tanzania. It is important to maintain that decrease of IPT discontinuation within three months following initiation to ensure PLHIV are protected against TB. The patients with advanced WHO clinical HIV stage, not on ART, male and patients with improved CD4+ cells/μL had higher chance of IPT discontinuation useful interventions to reduce the effects in these groups are needed. Forthcoming analysis of the routinely collected health data may monitor the changes in IPT discontinuation among PLHIV across zones in Tanzania. More research is needed on the effects of IPT discontinuation and its reasons covering large areas such as inter-zonal differences in Tanzania.

Declarations

Authors are declaring that this manuscript is our original work had never been submitted to any other journal for publication, and will not be submitted to any other for similar or any other for similar purpose. All source of information used have been acknowledged.

Availability of Data and Materials

The data that support the findings of this study are available from the Ministry of Health but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon request and with permission from Ministry of Health at National Aids, STIs and Hepatitis Control Program (NASHCOP).

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Authors' Contributions

Concept development and study design: MR, JT, WM, SEM, BN, JSN, MJM; Data acquisition: MR, VS, AR, WM; Supervision of the study: JT, WM, BN, JSN, MJM; Data analysis and statistical support: MR, JT, WM, BN, JSN, MRM, MJM, CCM, MN, MM; critically revised the manuscript: MR, SEM, JT, IJ, WM, BN, JSN, AR, MRM, MJM, CCM, MN, MM; All authors read and finally approved the manuscript draft for publication.

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