Determinants of Isoniazid Preventive Therapy Completion among People Living with HIV Attended Care and Treatment Clinics from 2013 to 2017 in Dar es Salaam Region,Tanzania. A cross-sectional analytical study

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Abstract

Background: Tuberculosis (TB) disease is a common opportunistic infection among people living with HIV (PLHIV). WHO recommends at least six months of isoniazid Preventive Therapy (IPT) to reduce the risk of active TB. It is important to monitor completion of IPT, as a suboptimal dose may not protect PLHIV from TB infection. This study determined IPT completion and its determinants among PLHIV aged 15 years or more in Dar es Salaam region, Tanzania.

Methods: A Cross-sectional analytical study was conducted using secondary analysis of routine data from 58 care and treatment clinics in Dar es Salaam region. The study recruited clients who screened negative for TB symptoms and initiated IPT between January 2013 and June 2017. Modified Poisson regression model with robust standard errors were used to estimate prevalence ratios (PR) and 95% confidence interval (CI) for factors associated with IPT completion. Multilevel analysis was used to account the health facility random effects in order to estimate independent factors associated with IPT completion.

Results : A total of 29,382 clients were initiated on IPT, with 21,808 (74%) female. Overall 17,092 (58%) completed IPT, increasing from 42% (773/1,857) in year 2013 to 76% (2,929/3,856) in 2017. Multilevel multivariable model accounting for health facility as clusters, found that clients with CD4 counts between 100 to 349 cells/ had 3% lower prevalence of IPT completion as compared to those with 100 cells/ (PR:0.97: 95%CI:0.94-1.01). Patients who were not on ART had 46% lower IPT completion compared to those were on ART (PR: 0.54: 95%CI: 0.45-0.64). There was lower IPT completion among clients who transferred to another clinic compared to those attended the same clinic where they were initiated IPT (PR: 0.63: 95% CI (0.54-0.74).

Conclusion: IPT completion is low at care and treatment clinics although it increased over time. Lower IPT completion was seen in PLHIV with CD4 counts between 100 to 349 cells/ , those who transferred to other clinics and those not on ART. Thus it indicates the need for better IPT interventions with greater support PLHIV in those groups.

Background

Tuberculosis (TB) disease is common among people living with HIV (PLHIV), with the lifetime risk of acquiring disease 20-37 times higher compared to people who are HIV negative (1–5). Tuberculosis co-infection increases the consequences of the HIV burden and contributes to 30-40% of deaths among PLHIV in high endemic regions (6–9). Globally TB/HIV co-infection is a major public health concern with more than1 million PLHIV co-infected with TB in the year 2017 (7,10), and 78% of those conifected with TB living in Africa (7). In Tanzania there were 142,000 new TB cases in 2018, and 34% of these TB cases were PLHIV (11–14).In Tanzania more than 1 million PLHIV attend care and treatment clinic, and in 96% of all clinic visits they are screened for TB (15). The consequences of TB/HIV co-infection is an increase

in mortality among PLHIV, with the worldwide estimate of 300,000 deaths among PLHIV co-infected with TB in 2013 and 400,000 in 2017 (3,7,8,11–14,16).

Isoniazid is the common name for isonicotinylhydrazide (INH) and is one of the drugs used for first line treatment for TB infection (17). Among PLHIV, INH is also used to prevent TB infection through the Isoniazid Preventive Therapy (IPT) intervention (10). In epidemiological studies from different countries, IPT has been shown to reduce risks of TB incidence occurrence by 33-90% among HIV infected people (7,10,18–27). WHO recommends the completion of at least six months IPT for the successful prevention of active tuberculosis among PLHIV (4,10). Globally, six-month IPT completion has been reported to range from 39-99%(28–37), and in Tanzania studies reported 65%-98% of those who initiated IPT, completed the six month treatment course (6,20,38–40). Most epidemiological studies have shown that IPT completion reduces the risks of mortality among PLHIV(8,26,41), decreases the need for expensive TB treatment needs and lowers the cost of HIV services. Successful use of IPT will help Tanzania achieve the sustainable development goals (SDG) by 2030 and is part of the national strategy to control TB in Tanzania (6,7,42,43). However, it shows that a good number of PLHIV do not complete the full six-month IPT treatment course and little is known about the determinants of IPT completion in routine HIV clinics settings. The iinformation on IPT completion would be useful to the Ministry of Health, Community Development, Gender, Elderly and Children (MOHCDGEC) in order to plan better interventions to prevent TB in among PLHIV (14,20,38,44–46).This study aimed to determine six-month IPT completion and factors associated with IPT completion among PLHIV aged 15 years or more in Dar es Salaam region, Tanzania.

Methods

A cross-section study using secondary analysis of de-identified routinely collected data from PLHIV attending HIV services in 58 care and treatment clinics (CTC) was conducted in Dar es Salaam region. The study retrieved data from the CTC electronic database, which is used for managing HIV patients clinically.

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 for TB and were initiated IPT between January 2013 and June 2017 were included in the analysis (Fig 1).

All subsequent clinic records of those who initiated IPT were reviewed for six-month IPT completion at their scheduled monthly visits. The outcome variable, six-month IPT completion, was defined as the collection of IPT drugs for the full six months following initiation. The independent variables were sex, age, functional status, pregnancy status, marital status, ART status, WHO clinical stage as well as CD4 count cells/μL at IPT initiation. The study used the records of all patients who initiated IPT in care and treatment centres (CTC) from all health facilities in Dar es Salaam region from January 2013 to June 2017. Figure 1 shows the total clients enrolled in HIV care, and the exclusion for different reasons (fig.1).

Data analysis was performed using STATA version 15.0 (STATA Corp, College station, TX). Descriptive statistics were summarized using means, standard deviation (SD)) and medians (IQR) for continuous variables; frequency and proportion for category variables. The chi-square test was used to compare the differences in the proportion of completing IPT across the patient characteristics. A modified Poisson regression model was used to determine the prevalence ratio (PR) and 95% confidence interval (95% CI) of factors associated with IPT completion. Multilevel modelling was used to estimate the independent determinants of IPT completion, while accounting for the dependency of individuals within health facilities. Intra class correlation was used to measure the proportion of variability explained by the between health facilities variation.

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 Control Program (NACP), which owns the data on behalf of MoHCDGEC. 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 PLHIV, 124,747 (88.7%) had record of a negative TB screening results. Of those who screened negative 51,266 (41%) initiated IPT, we excluded 6,700 (13.1%) who were aged less than 15 years and 15,184 who initiated after 1st June 2017, leaving a total of 29,382 PLHIV in the analysis (Fig 1).

The demographic and clinical characteristics of the 29,382 participants who initiated IPT are shown in table 1 with 21,808 (74.2%) female, and a mean age of 41.4 years (standard deviation SD: 10.2) (Table1.). The majority 28,859 (98.2%) were on ART, and the median CD4 counts was 155 cells/μL (interquartile range (IQR): 48-260), although a large group 13,687 (46.8%) had CD4 counts less than 100 cells/μL. Majority 28,480 (97.1%) PLHIV were actively attending clinics and 26,512 (90.3%) were attending in their scheduled appointment dates (table1).

Prevalence of Isoniazid Preventive Therapy completion

Over the period January 2013 to December 2017, the overall IPT completion prevalence was 58%, but the IPT completion increased from 42% in 2013 to 76% in 2017 (Fig.2).

Factors associated with Isoniazid Preventive Therapy completion

Univariate analysis accounting health facility random effects, indicated that the six-month IPT completion was 50% lower among those who were not on ART (PR: 0.50: 95%CI: 0.42-0.59) compared to

those were on ART (Table 3). PLHIV who received IPT at private clinics had a 16% higher prevalence of IPT completion compared to those in public health facilities (PR: 1.16: 95%CI: 0.99-1.36) although this was statistically non-significant. PLHIV with stage III (PR: 0.1.01: 95%CI: 0.96-1.04) and stage IV (PR: 0.99: 95%CI: 0.93-1.06) were less likely to complete IPT compared to those with Stage 1 or Stage II HIV disease. PLHIV with high CD4 counts of ≥350 cells/μL had a 6% lower IPT completion rate (PR: 0.94: 95%CI: 0.90-0.98) compared to those with CD4 count <100 cells/μL.

Multivariate multilevel analysis after adjusting all variables which were statistically significant at univariate analysis, had clinical meaning and potential confounders by priori. The variables which were adjusted are age, sex, year of IPT initiation, ART status, clinical stage (important variable), CD4 counts in cells/μL and client visit status as well as accounting the random effects due to specific health facility. The adjusted PR shows patients not on ART had a 46% lower IPT completion when compared to those not on ART (APR: 0.54: 95%CI: 0.45-0.64). PLHIV who transferred to other clinics within Dar es Salaam region had 37% lower IPT completion compared to those were attending in the same clinics (APR:0.63: 95%CI:0.54-0.74). Compared to 2013 the prevalence of completing IPT was 24% higher in 2016 (APR:1.24: 95%CI: 1.14-1.36) and 34% higher in 2017 (APR:1.34: 95%: 1.22-1.47). The IPT completion rate was 6% lower among PLHIV aged 25-34 years compared to those aged 15 to 24 years (APR:0.94: 95%CI:0.89-0.98). The random effects results showed that 5.8% of the variability in IPT completion was due to differences between health facilities (Table3).

Discussion

These data show the completion of IPT among PLHIV who are attending routine HIV services in Dar-es-Salaam, Tanzania. The overall IPT completion was 58% and it increased over the four years from 42% in 2013 to 76% in 2017. This probably reflects the improved HIV services provided in the health facilities in Tanzania with better linkage between TB and HIV services, increased HIV testing and immediate ART initiation for those testing positive (47). Since 2013 TB and HIV services have been devolved to lower level health facility in Tanzania (47).

Among the clients who did not complete IPT in the recommended period of six months, 96.2% discontinued IPT within the first three months of initiation. This is consistent with findings from Malawi, Zimbabwe and Ethiopia, which showed of those who stopped, 85%, 89% and 89% respectively stopped in the first month (32,48,49). Patients may be discouraged by the long treatment duration of IPT and the need to attend clinic every month (32,48,49). Interventions have been considered to help new patients in those first few months, such as automated mobile phone short message services (SMS), smart-phone applications and home visits by lay counsellors as these have been shown to be effective in Malawi (49).

PLHIV who were transferred to another clinics within Dar es Salaam region after IPT initiation had significantly lower IPT completion as compared to those attended the same clinic for the whole six months. This result is similar to the findings from Zimbabwe and Ethiopia(27,32). The significantly higher IPT completion rate among PLHIV on ART is consistent with results obtained in Kenya, Zimbabwe and

Brazil(30,32,37). These results indicate that patients who are already linked with ART services have an increased prevalence of IPT completion. The significantly lower prevalence of IPT completion among those aged 25-34 years compared to those aged 15-24 years was consistent with a study in Uganda, but contrary to the results from Malawi (36,49). HIV patients with high CD4 counts ≥350 cells/μL had lower prevalence of IPT completion compared with those with CD4 counts <100 cells/μL. This is consistent with studies in Kenya and Brazil (30,37). Possibly patients with high CD4 counts perceive themselves healthy and not at risk of progressing to active TB, so they stop taking IPT before completing the full treatment course of six months.

There was non-significant lower IPT completion among clients with advanced stage HIV disease, as shown by PLHIV with low CD4 counts, differed from findings from a study in Malawi (48). PLHIV with advanced HIV stage are at higher risk of death which would be a reason for them not completing IPT although this was not statistically significant in a study in Zimbabwe (32). PLHIV attending private health facilities had higher IPT completion compared to those attending public facilities althouhg this was not significant in this analysis. The differential might imply socio-economic inequities and difference in services costs between private and public health facilities, which was shown to influence IPT completion in Jamaica and Uganda(36,50). Although Tanzanian guidelines for HIV services cover both public and private facilities, more could be done to harmonize the practice styles and skills between private and public clinics.

Strenghs and limitations of the study

The study had large sample size and high power ≥ 90% to detect the true association between IPT completion and with its determinants. The study used routinely collected data, which reflected the real practices in Dar es Salaam, and the same analysis can be incorporated into regular analyses of the CTC data across Tanzania. The study included longer time interval which helped to account for population changes since IPT program was rollout in Tanzania. The study used modified Poisson regression, with robust standard errors, to avoid biases 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 incompleteness and missing data which might have underestimated or overestimated the estimated prevalence ratios of IPT completion. Another limitation is that the study used routinely collected data which are collected for patient mangaement and programatic purposes, and not for research puporses. Therefore some important variables which are possibly associated with IPT completion are not routinely collected and recorded in the CTC2 database.

Conclusions

IPT completion rate prevalence in Dar es Salaam region was low in 2013 but increased over time. This corresponds with a general improvement in HIV services, and the monitoring and evaluation of HIV services in Tanzania. It is important to maintain that increase to ensure people living with HIV are protected against TB disease. Targeted interventions need to be developed to assist patients with lower

IPT completion. Further analysis of routinely collected health data should be done to monitor the changes in IPT completion among PLHIV. More research is needed on the effects of IPT non-completion rate and the reasons for non-completion among PLHIV who initiate IPT 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.

Abbreviations

CPR: Crude prevalence ratio;

APR: Adjusted prevalence ratio;

ART: Antiretroviral therapy;

CI: confidence interval;

CTC: Care and treatment clinics;

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

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Availability of data and materials

The data that support the findings of this study are available from the Ministry of Health Community Development Gender Elderly and Children (MOHCDGEC) 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 MOHCDGEC.

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; critically revised the manuscript: MR, SEM, JT, IJ, WM, BN, JSN, AR, MRM, MJM; All authors read and finally approved the manuscript draft for publication.

Ethics approval and consent to participate

Ethical approval was obtained from the Kilimanjaro Christian Medical University College (KCMUCo). The secondary data use deemed unnecessary need of informed consent because did not have any identifier and it was unlinked from the database. Permission to use CTC data was sought from the MoHCDGEC through the National Aids Control Program (NACP).

Consent for publication

The permission to publish the data was obtained from NIMR after informed about findings of the study while the permission to use CTC2 data was sought from NACP after being fully informed about the objectives.

Competing interests

The authors declare that they have no competing interests

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Tables

Table1.Demographic and Clinical characteristics of 29,382 Participants Attending HIV Services in Dar es Salaam Region

Variable	Frequency	%	IPT completers N=17,092(58.2)	P-value
Age category				
15-24	1454	4.9	818(56.3)	
25-34	5216	17.8	2,999(57.5)	
35-44	11708	39.9	6,771(57.8)	
≥45	11004	37.4	6,504(59.1)	
Mean(standard deviation)	41.4(±10.2)		41.55(±10.1)	0.053
Sex				
Male	7574	25.8	12,702(58.2)	
Female	21808	74.2	4,390(57.9)	0.667
Marital status (n=25888)				
Single	7847	30.3	4,414(56.2)	
Married/cohabiting	13401	51.8	7,945(59.3)	
Divorced/widowed	4640	17.9	2,823(60.8)	<0.001
Year of Initiation				
2013	1857	6.3	773(41.6)	
2014	5169	17.6	2,254(43.6)	
2015	7754	26.4	3,783(48.8)	
2016	10746	36.6	7,353(68.4)	
2017 (Jan to June only)	3856	13.1	2,929(75.9)	<0.001
PLHIV by Health facility ownership				
Public	20272	68.9	10,699(52.8)	
Private	9110	31.1	6,393(70.2)	<0.001
ART status (n=29374)				
Not on ART	515	1.8	136(26.4)	
On ART	28859	98.2	16,956(58.7)	<0.001
WHO clinical stage (n=29121)				
I	5026	17.3	3,141(62.5)	
II	6758	23.2	4,017(59.4)	
III	14910	51.2	8,505(57.1)	
IV	2427	8.3	1,348(55.5)	<0.001
CD4 count in cells/µL **(n=29249)**				
<100	13687	46.8	8,001(58.5)	
100-349	9927	33.9	5,999(60.4)	
≥350	5635	19.3	3,016(53.5)	<0.001
Median (lower quartile, upper quartile)	155(48, 260)			
Visit status (n=29337)				
Actively attending clinics	28480	97.1	16,720(58.7)	
Missing scheduled appointments	383	1.3	186(48.6)	
Transferred to another clinic	474	1.6	174(36.7)	<0.001
Co-medications (n=10047)				
Cotrimoxazole	7180	71.5	4,160(57.9)	
Fluconazole	22	0.2	9(40.9)	
Others	2845	28.3	1,743(61.3)	0.002
Visit type (n=29354)				
Scheduled	26512	90.3	15,435(58.2)	
Traced back after LTFU	238	0.8	161(67.7)	
Treatment supported drugs pick up	287	1.0	174(60.6)	
Unscheduled	2317	7.9	1,309(56.5)	0.007

Key: n-small sample size, *N=number of patients, LTFU-Lost to follow up, ART-Antiretroviral, IPT-Isoniazid Preventive Therapy, PLHIV-People living with HIV,*

Table3.Determinants of IPT completion 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	0.97(0.90-1.05)	8.5%	0.439	0.97(0.89-1.04)	0.336	
25-34	0.94(0.89-0.98)		0.003	0.94(0.89-0.98)	0.010	
35-44	0.97(0.94-1.01)		0.091	0.97(0.94-1.01)	0.182	
≥45	Reference			Reference		
Sex						
Female	Reference			Reference		
Male	1.01(0.97-1.04)	8.5%	0.710	0.99(0.96-1.03)	0.876	
Years of IPT						
2013	Reference			Reference		
2014	0.93(0.85-1.02)		0.121	0.92(0.84-1.02)	0.101	
2015	0.98(0.89-1.08)		0.736	0.98(0.89-1.07)	0.621	
2016	1.26(1.16-1.38)		<0.001	1.24(1.14-1.36)	<0.001	
2017	1.37(1.25-1.50)	6.3%	<0.001	1.34(1.22-1.47)	<0.001	
Marital status						
Married/cohabiting	Reference			Reference		
Single	0.98(0.95-1.02)		0.384			
Divorced/widowed	1.01(0.96-1.05)	8.5%	0.944			
Health facility ownership						
Public	Reference			Reference		
Private	1.16(0.99-1.36)	7.9%	0.067	1.11(0.97-1.26)	0.144	
ARV status						
On ARV	Reference			Reference		
Not on ARV	0.50(0.42-0.59)	8.3%	<0.001	0.54(0.45-0.64)	<0.001	
WHO stage						
I	Reference			Reference		
II	0.98(0.94-1.03)		0.553	0.98(0.94-1.04)	0.613	
III	1.01(0.96-1.04)		0.986	0.98(0.94-1.02)	0.376	
IV	0.99(0.93-1.06)	8.4%	0.907	0.97(0.91-1.04)	0.455	
CD4 counts in cells/						
<100	Reference			Reference		
100-349	0.96(0.93-0.99)		0.022	0.97(0.94-1.01)	0.083	
≥350	0.94(0.90-0.98)	8.5%	0.007	0.96(0.92-1.01)	0.085	
Client visit status						
Attending in the clinics at which client was initially enrolled in HIV care	Reference			Reference		
Missing appointments	0.87(0.76-1.01)		0.068	0.88(0.76-1.02)	0.098	
Transferred to another clinics within Dar es Salaam	0.63(0.60-0.71)	8.5%	<0.001	0.63(0.54-0.74)	<0.001	5.8%

Key: CPR-Crude prevalence ratio, CI-Confidence interval and APR-Adjusted prevalence ratio; ICC: Intra cluster correlation

Other adjusted covariates are: functional status and visit type

Figures

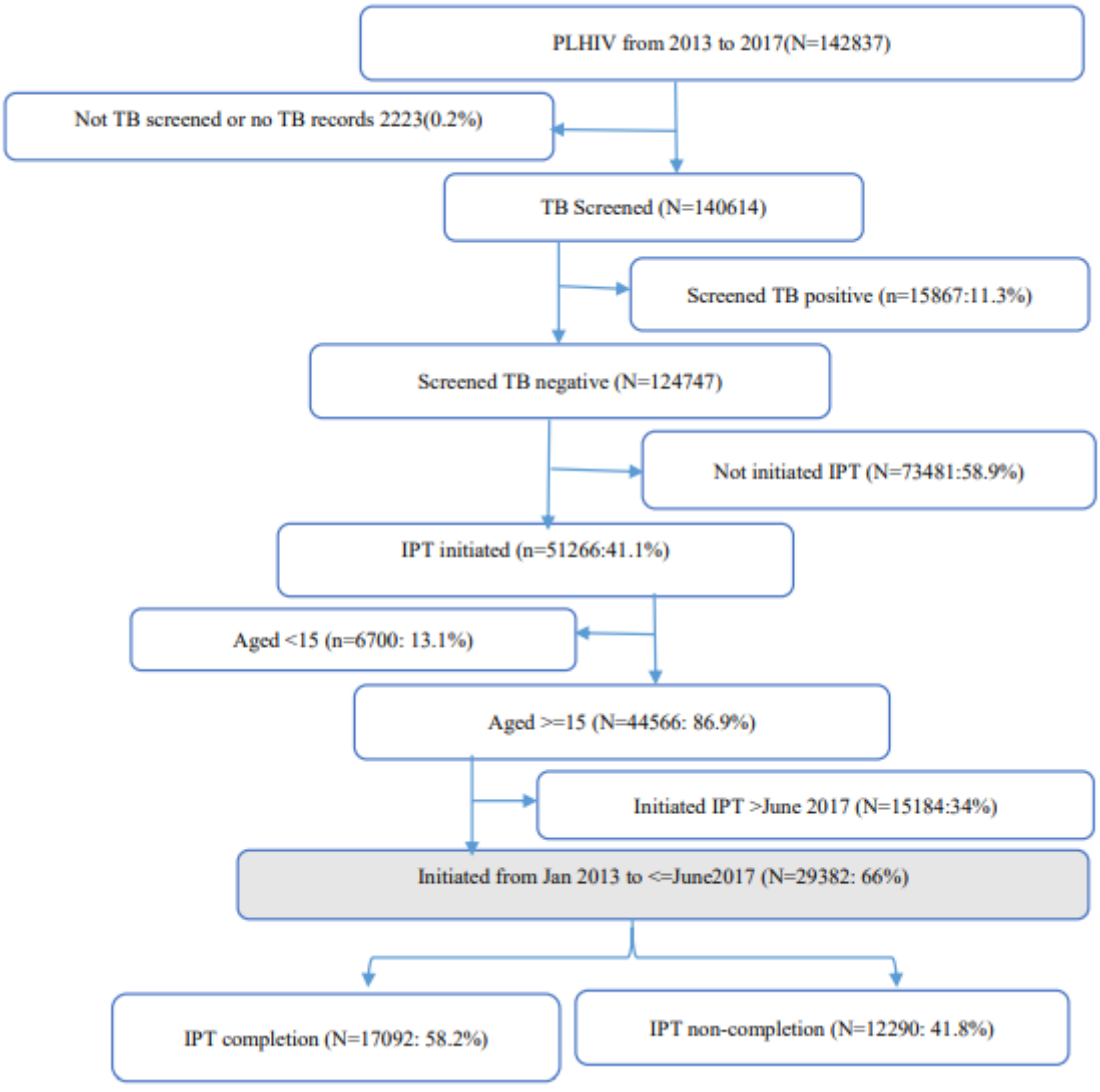

Figure 1

Flow chart determining how participants were selected

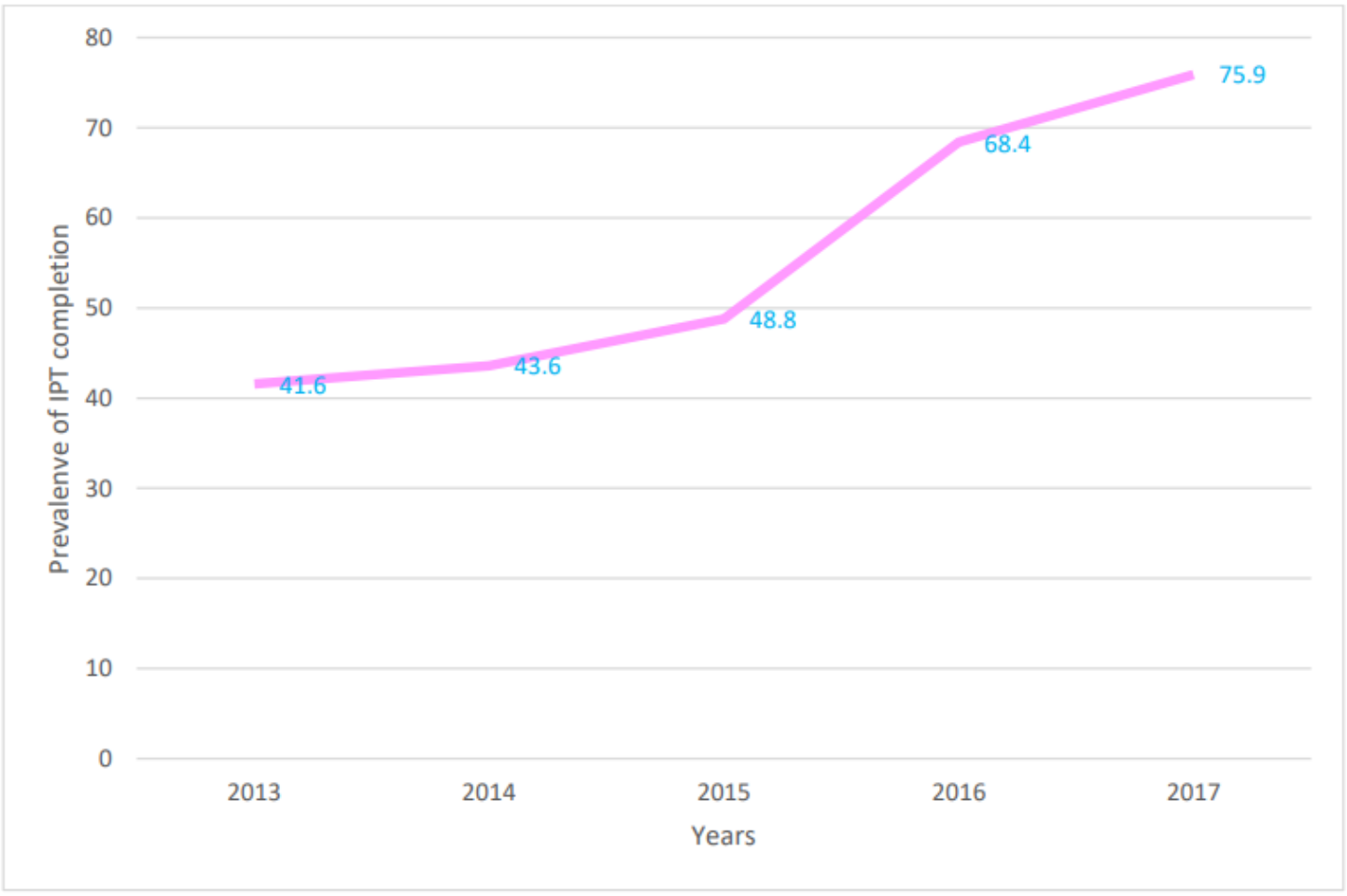

Figure 2

Trend of IPT completion prevalence by years