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Adherence to isoniazid preventive therapy and its determinants among people living with HIV

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***Abstract*---**Aims: To determine adherence levels to Isoniazid preventive therapy (IPT) and the factors influencing it in people living with HIV (PLHIV). Materials and Methods: An institution based descriptive longitudinal study was conducted from September 2017 to June 2019 to assess the level of adherence to IPT and its determinants among HIV patients. A total of 320 participants were included from the associated ART centres. Adherence was defined as completion of the 6-month course of treatment with 80% pills taken

and was measured by self -report of intake of tablets. Proforma and a semi-structured questionnaire was used to collect all the relevant information. Questionnaire covered aspects on TB treatment and care, HIV related stigma, medical provider relations, social support and socioeconomic status. Data was analysed using SPSS version 11.5. Results/ Discussion: IPT Adherence rate was 83.75 %. Of the 320 patients, 268 were adherent. Isoniazid related side effects were reported by 50 people, 33 of whom were withdrawn. Prior history of TB was noted in 43 people. Patients cited counselling and physician's advice on IPT intake as one of the main reasons for good adherence. Forgetfulness was the most common reason for missed pills. HIV related stigma was high but did not have significant impact on adherence. Conclusion: The level of adherence to IPT was high. Assessing adherence to IPT and its predictors is essential for its successful outcome in effectively mitigating the threat of TB coinfection. Counselling and patient education should be more strengthened through the entirety of regimen for consistent results. Comprehensive care and support, sustainable drug supply, evaluation of side effects and frequent reminders to take tablets is necessitated.

***Keywords*---**isoniazid, preventive therapy, determinants, HIV.

Introduction

Tuberculosis is by far the most common life-threatening opportunistic infection among people living with HIV (PLHIV) and it remains as the main cause of morbidity and mortality, including those on ART.[1][2][3] The proposed risk of acquiring TB is around 21 times greater in PLHIV as compared to those who do not have HIV infection.[2] The occurrence of TB in HIV poses a serious health problem due to the synergistic and bidirectional nature of the diseases. Such a co-infection can also lead to swift progression of HIV and worsen the prognosis. [4][5]. In light of this, three "I's" have been adopted nationally and internationally to tackle the rising burden of TB amongst PLHIV. These are:

- "INTENSIVE CASE FINDING"
- "INFECTION CONTROL"
- "ISONIAZID PREVENTION THERAPY"[6]

Multiple studies have demonstrated the role and benefit of IPT in significantly reducing the development of TB in HIV[7][8][9][10][11][12][13]. IPT is a key public health intervention in preventing TB in PLHIV.[2] It has formed a core component in HIV prevention & care, and WHO guidelines strongly recommend its implementation along with ART.[2]. The "National framework for HIV-TB collaborative activities (Nov-2013)" and "Standards of Tuberculosis care in India" recommended IPT as one of the important strategies for prevention of TB among PLHIV. The "Ministry of Health and Family Welfare" released an operational manual for Isoniazid

preventive therapy (IPT) through NACO in June 2016 following which IPT was implemented across India.[6]

However, its implementation has faced many barriers and has not progressed as expected. This has been due to factors such as concerns over adherence, side-effects and resistance.[2] [14] Since IPT is a preventive therapy measure, non-adherence to it affects the individual's own future risk of acquiring TB. Successful IPT was considered adherence >80% as per WHO guidelines 2011. However, this strongly suggests that concerns over adherence must not be a barrier in implementing IPT.[15] Thus, adherence rates must not be used to determine if IPT should be initiated. Instead, they should bring attention to the issue of why adherence rates are low, thus allowing for this information to be used upon to improve adherence to TB treatment. This study makes an attempt to bridge the knowledge gap by determining adherence to IPT and the factors contributing to it among people living with HIV, so as to address patients concerns about IPT as well as to enable those affected by HIV to benefit the most from this life saving intervention.

Materials and Methods

This was an institution based descriptive longitudinal observational study conducted in associated ART centres between September 2017 to august 2019. The study subjects were all HIV positive people at associated ART centres who had been started on IPT. PLHIV who were less than 18 years of age and who had prior history of liver disease, peripheral neuropathy, or past history of adverse drug reactions to isoniazid were excluded. A sample size of 320 participants was considered after running the relevant statistical analysis. Study was initiated after obtaining approval from the Institutional Ethics Committee. The questionnaire used in the study was standardised and validated (Cronbach's alpha> 0.7) as per protocol after running a pilot study and making the relevant changes to the questionnaire. Adherence was calculated based on number of pills taken /no. of pills to be taken *100. Data collection comprised mainly of 3 parts

- Adherence at 6 months was determined from patient records at the respective ART centre and self-reported adherence.
- A Proforma was used to assess baseline characteristics of study subjects.
- A semi structured questionnaire was used to collect all the relevant details relating to the study at the end of 6 months.

Socioeconomic details were assessed using "Kuppuswamy's socioeconomic status scale" revised for 2016. Data was analysed using "SPSS (statistical package for social sciences) version 11.5". Categorical variables were analysed and compared using chi square test. P value<0.05 was considered as statistically significant.

Results

Adherence rate was found to be 83.75%. Out of 320 people, 268 (83.75%) people were found to be adherent (IPT intake of >80 %). Majority were on TLE regimen (240) followed by ZLN regimen (63). Out of 320 study participants, 175 were male and 145 were female. As depicted in Table 1, demographic factors like age, sex,

BMI, SES (Socio-economic Status), marital status, social support and distance from ART centre have a considerable impact on adherence. Among the participants, <30 years of age had 90.9%(n=20) adherence whereas participants in the age group of 31-50 93.4%(n=198) showed adherence. Participants who were >50 years of age showed 94.33%(n=50) adherence. Among the females, 94.4%(n=118) were adherent and among males, 92.6% (n=150) were adherent. Among the participants of the middle SES, 94.5%(n=120) were adherent while participants of low SES, 92.5%(n=148) showed adherence. Divorced people had the lowest adherence, showing 85.71%(n=18) adherence rate. Participants who had social support, 95.43%(n=251) had good adherence and those who did not have social support, 70.83%(n=17) were adherent. Participants who lived far from the ART centre, 60%(n=6) were adherent and among those who had no problem with the distance, showed 94.58%(n=262) adherence.

As depicted in Table 2, among those people who had HIV for <10 years, 91.94%(n=217) were adherent and those who had for >10 years 100%(n=51) showed adherence. CD4 counts also seem to play a viable role in adherence, participants with CD4 counts <500, have shown 92.3%(n=108) adherence and people with CD4 counts >500, have shown 94.11% (n=160) adherence. Among the participants with VAS scores <5, 36%(n=36) were adherent and those with >5, 97.47%(n=232) were adherent. As seen in Table 3, certain personal factors like forgetfulness, habits and pill burden showed significant effect on IPT adherence. 60.46%(n=26) of participants forgot to take their drugs, whereas of those who may or may not have forgotten, 91.3%(n=21) were adherent. Participants with history of alcohol consumption, 87.8%(n=36) were adherent; with history of smoking, 100%(n=20) were adherent whereas those who had history of both alcohol and smoking 82.85%(n=29) were adherent and those who had no such habits 95.81%(n=183) were adherent. Among the participants who complained of pill burden, 25%(n=3) were adherent and those who did not complain, 96.36%(n=265) were adherent. Participants who had disclosed their HIV status, 93.6% (n=249) showed adherence as compared to those who had not disclosed their status among who, 90.47%(n=19) were adherent. Among those participants with HIV related stigma, 93.22%(n=165) were adherent, whereas participants without any stigma (n=2), 100% showed adherence, whereas those who may or may not have a stigma, 93.51%(n=101) were adherent. Among participants who disclosed their IPT status, 93.68%(n=178) were adherent whereas those who did not disclose their status, 92.78%(n=90) were adherent.

As seen in Table 4, among participants who were aware about IPT, 95.03% (n=268) were adherent. Among participants who were explained the IPT by the doctor, 95.81% (n=252) were adherent while those who were not explained by the doctor, 66.6% (n=16) were adherent. Among participants who received counselling from health workers regarding IPT and its importance, 94.3%(n=265) were adherent and those who did not receive it 50%(n=3) were adherent. Patients who had knowledge about IPT in TB prevention, 96.52%(n=250) were adherent whereas those who did not know 64.28%(n=18) were adherent. There were participants in the study who were not sure whether IPT is dangerous and they showed 76.47%(n=39) adherence rate whereas those who had no such opinion showed 97.03%(n=229) adherence rate. Among participants who were counselled on adherence, 94.36%(n=268) were adherent. Among participants who thought

being asymptomatic affected IPT, 20%(n=1) were adherent, those who did not think the same, 100%(n=256) were adherent whereas those who were not sure about it, 42.3%(n=11) were adherent. Of patients who regularly came for their follow up visits, 98.1%(n=259) were adherent whereas those who did not come regularly, 39.13%(n=9) were adherent. Among participants who benefitted from doctor's advice, 100%(n=258) were adherent whereas those who may or may not have benefitted from advice, 35.71%(n=10) were adherent.

A total of 43 participants had prior history of TB, out of which 34 had pulmonary TB, 3 had abdominal TB, 5 had TB lymph node and 1 had TB meningitis. 277 participants had no prior history of TB. About 74 participants had comorbidities while 246 had no comorbidities. Out of 320, 50 had side effects, 33 of whom had to be stopped on IPT. A total of 52 participants were non - adherent, out of which 19 people finished their 6-month IPT course and had adherence < 80% whereas 33 people had to be stopped for medical reasons during the course of IPT because of side effects. People who had been stopped on IPT were not taken into account for the comparative analysis across different variables between adherent and non-adherent individuals. Further comparative analysis only involved 287 participants who had completed IPT course. Mean adherence among people (n=287) who took tablets for 6 months was found to be 95.11%.

Table 1
Association of demographic factors with IPT adherence (n=268)

Variables		Adherent (n=268)		Non-adherent (n=19)		***P*** value
		n	%	n	%	
Age	<30	20	90.9	2	9.09	0.836
	31-50	198	93.4	14	6.6	
	>50	50	94.33	3	5.66	
Sex	Male	150	92.6	12	7.4	0.541
	Female	118	94.4	7	5.6	
BMI	Underweight	59	92.19	5	7.81	0.122
	Normal	171	93.95	11	6.04	
	Overweight	30	96.77	1	3.22	
	Obese	8	80	2	20	
SES	Low	148	92.5	12	7.6	0.501
	Middle	120	94.5	7	5.5	
Marital	Married	186	94.41	11	5.58	0.398
	Widow	36	92.3	3	7.7	
	divorced	18	85.71	3	14.28	
	Single	28	93.33	2	6.66	
Support	Yes	251	95.43	12	4.56	<0.0001
	No	17	70.83	7	29.16	
Distance being difficult	Yes	6	60	4	40	0.002
	No	262	94.58	15	5.41	

Table 2
Association of HIV follow-up related factors with IPT adherence (n=268)

Variables		Adherent (n=268)		Non-adherent (n=19)		***P*** value
		n	%	n	%	
HIV duration	<10	217	91.94	19	8.05	0.03
	>10	51	100	0	0	
ART duration	<5	140	93.33	10	6.66	0.974
	>5	128	93.43	9	6.56	
CD4	<500	108	92.3	9	7.7	0.545
	>500	160	94.11	10	5.88	
TB history	Yes	43	100	0	0	0.088
	No	225	92.21	19	7.78	
VAS	<5	36	73.46	13	26.53	<0.0001
	>5	232	97.47	6	2.52	

Table 3
Association of Personal factors with IPT adherence (n=268)

Variables		Adherent (n=268)		Non-adherent (n=19)		***P*** value
		n	%	n	%	
Forgetfulness	Yes	26	60.46	17	39.53	<0.0001
	No	221	100	0	0	
	Maybe	21	91.3	2	8.7	
Habits	Nil	183	95.81	8	4.18	0.01
	Alcohol	36	87.8	5	12.2	
	smoking	20	100	0	0	
	Both	29	82.85	6	17.14	
Pill burden	Yes	3	25	9	75	<0.0001
	No	265	96.36	10	3.63	
IPT disclosure	Yes	178	93.68	12	6.31	0.772
	No	90	92.78	7	7.21	
HIV disclosure	Yes	249	93.6	17	6.39	0.638
	No	19	90.47	2	9.52	
HIV related stigma	Yes	165	93.22	12	6.78	1.000
	No	2	100	0	0	
	Maybe	101	93.51	7	6.48	

Table 4
Association of Counselling factors with IPT adherence (n=268)

Variables		Adherent (n=268)		Non-adherent (n=19)		***P*** value
		n	%	n	%	
Awareness about IPT	Yes	268	95.03	14	4.96	<0.0001
	No	0	0	5	100	

Treating doctor explained	Yes	252	95.81	11	4.18	<0.0001
	No	16	66.6	8	33.3	
Health worker explained	Yes	265	94.3	16	5.7	0.004
	No	3	50	3	50	
IPT prevents TB	Yes	250	96.52	9	3.47	<0.0001
	No/not sure	18	64.28	10	35.71	
IPT is dangerous	Yes	0	0	0	0	<0.0001
	No	229	97.03	7	2.96	
	Not sure	39	76.47	12	23.52	
Counselled on were adherent	Yes	268	94.36	16	5.63	<0.0001
	No	0	0	3	100	
Being Asymptomatic affected IPT	Yes	1	20	4	80	<0.0001
	No	256	100	0	0	
	Maybe	11	42.3	15	57.7	
Regular follow up	Yes	259	98.1	5	1.89	<0.0001
	No	9	39.13	14	60.87	
Doctors advise helped	Yes	258	100	0	0	<0.0001
	No	0	0	1	100	
	Maybe	10	35.71	18	64.28	

Discussion

Of the 320 participants in the study, 83.75 % (n=268) people were found to be adherent (IPT intake of >80 %). A study conducted on IPT adherence in 2011 by Mindachew *et al*, on 319 people showed a mean adherence of 86.5%[16]. Ayele *et al* in 2017 found adherence rates of 90.3% among 154 participants[17]. Getachew *et al* in 2017 found Adherence to INH was 94% among 403 participants [18]. Abdulalim *et al* in 2017 conducted a study on 168 PLHIV and adherence was at 68.5%[19] A study done by Berhe *et al* in 2014 showed adherence rates of 89.5% among 381 participants.[20] All these above studies assessed adherence based on self-reported intake of INH tablets taken over the past 7 days. A study done in 1996 by Ngamvithayapong *et al* among 412 participants found that adherence rates were 67.5 %. This study differed from other studies as adherence was assessed over a 9 month period and INH intake was assessed by pill count.[14]

Ayele *et al* in 2016 showed that of 162 PLHIV included, 64.2% (n=104) were adherent to IPT. This differed from other studies by having a higher cut off for food adherence. Having an adherence of 90% over 6 months counted for good adherence unlike other studies which had used the criteria of 80% and above to classify the adherence as good. Adherence in this study was quantified using diary record as well as pill count.[21] In our study we used the WHO recommended 80% cut off as good adherence and adherence rate data collection was done by seeing the monthly documented adherence in ART cards alongside self-reported adherence at the end of 6 months. Y Mueller *et al.* (2017) assessed 252 PLHIV over the course of 36 months in a high prevalence setting and found good adherence rates. The assessment of IPT adherence by Mueller had its strengths compared to other studies as it combined pill count, self-reported lack of intake in number of days over the last 14 days, the “Morisky scale” and quantitative

evidence in the form of urine testing for INH. [22] However, it must be noted that the same is not feasible in every setting.

Good adherence rates were noted in our study and in in agreement to some of these earlier studies. Our study was in agreeance with prior literature, and noted good adherence rates amongst the participants. Out of the total 320 participants, 52 were non-adherent. In this proportion, 19 finished their 6-month IPT course and were <80% adherent to the therapy, whereas 33 had to stop IPT due to toxicity and side effects. In earlier studies, even people who had been stopped due to adverse drug reactions were involved in comparative analysis. Ayele *et al* found in their 2016 study that adherence for such people was calculated by the percentage of pills taken during the period until IPT discontinuation.[21] However, in our study although the 33 PLHIV who had discontinued IPT were accounted for non-adherence, they were omitted in the comparative analysis for other variables so as to better see a relation and interplay between the various factors in influencing IPT.

Mean adherence among people (n=287) who took tablets for 6 months was found to be 95.11%. As seen in Table 1 to Table 5, categorical variables were analysed across two groups and adherence levels were noted to improve with age. Adherence levels were marginally higher in females. It was better among normal and overweight people compared to other extremes of the BMI spectrum. Lowest levels of adherence noted in obese people. When taking into consideration socioeconomic status, higher adherence rates were noted amongst middle class participants compared to lower class. Adherence levels were lowest amongst divorced people and with marital discord than others. Although all of the above categorical variables showed differences in adherence rates among the patients, they were not statistically significant. The effect of social support on adherence was found to be highly significant, as a higher proportion of good adherence was seen in those that received social support compared to those without. Distance to the ART centre also seemed to be a factor affecting adherence to the IPT regimen as it was poorer amongst those who had difficulty reaching the centres.

People who had had a positive HIV status for at least 10 years had greater adherence than those who had had a positive HIV status for less than 10 years. It was also seen that those who had a past history of TB had higher rates of adherence than the ones who did not. These aforementioned differences, although notable, were not statistically significant. One interesting observation was that of those who had had a past history of TB, not a single person fell into the poor adherence category. It could be postulated that an earlier exposure to TB in the past and its treatment could have probably prepared them with the knowledge and awareness about TB and INH. The “Visual analog scale” where the participants subjectively rated their quality of life was paired up with both groups. A clear statistical significance was seen among people with higher VAS score and higher VAS scores were seen among those who were adherent to IPT.

It was found that parameters concerning awareness and knowledge about IPT as well as briefing on IPT by physicians and health care workers all seemed to rate higher among the adherence group than non-adherent group with a high statistical significance. Physicians’ advice on taking IPT and counselling on

adherence by heath workers also seemed to improve adherence to therapy as a high statistical significance was noted. Pill burden was also found to be a factor that was statistically significant as a greater proportion of the (n=9) non-adherent population complained of the pill burden being present. A good number of people who were adherent felt good having started IPT. They noted changes such as increased weight gain and in their CD4 count.

Patients who noted instances of forgetfulness or being asymptomatic also seemed to have missed tablets and as a result have poor adherence. HIV disclosure rates were higher in comparison to IPT disclosure. HIV related stigma was widely noted in both populations, however didn't affect adherence to IPT. Continuous variables were analysed further using t-test as seen from Table 6. Both HIV duration and ART duration in mean years were noted to be higher amongst adherent group than non-adherent, which was found to be statistically significant. This corroborates well with the analysis of categorical variables as higher duration of HIV correlated with better adherence. Mean VAS score was also noted to be higher amongst adherent individuals, which was very high statistically significant. Of the 33 patients who had to discontinue their treatment during the course of IPT, the most common side effect noted by the patient was of general malaise (n=10). The second most common side effect was vomiting and gastritis, of which 6 participants complained. 4 patients had jaundice, and 4 experienced peripheral neuropathies. 1 patient developed abdominal pain. 1 patient discontinued therapy citing mastalgia as their complaint. They had a history of cyclical mastalgia and IPT precipitated the same and worsened the condition in this patient.

A patient with a history of a psychiatric disorder had to stop INH due to a worsening of their psychosis. On review of literature for such an instance, one similar event was noted in a study by Mueller *et al* (2017) which had one similar case of psychotic decompensation following IPT and in view of which IPT had to be duly stopped.[22] Ayele *et al* found in 2017 that INH-related side effects were reported by 48 (31.2%) among 154 participants, of which the most common were abdominal pain, vomiting, skin rash, jaundice, and numbness. Only 3 of these 48 people halted IPT as rest continued taking INH in the presence of mild side effects.[17]. Similar findings were also seen in study by Getachew *et al* (2015) where 142 out of 403 people experienced side effects, of which vomiting was the most common but only 53 among the 142 actually discontinued IPT. [18]. Contrastingly, in our study a majority of people who experienced side effects stopped INH. Health care workers advice may have a role to play in this. The threshold for discontinuation of IPT in the wake of any symptoms may have been lower in our setting given the fact that IPT is mainly a preventive therapy.

All the prior literature on IPT adherence show a common pattern for poor adherence. Factors such as IPT related side effects, forgetfulness, lack of advice, HIV stigma, ART facility being far away accounted for poor adherence at differing rates in different studies. Factors such as awareness and knowledge about IPT, good counselling, regular follow ups, treating physicians advise, TB related knowledge and good social support facilitated IPT intake and adherence. Physician advice as a facilitator for adherence was noted in studies by Abdulalim *et al* and Berhe *et al* [19][20]. Social support as a facilitator was noted in a study by

Tram *et al*[23]. Good medical provider relationships were found to be a positive factor in a study conducted by Ngamvithayapong *et al.*[14]

Numerous studies have shown awareness about IPT and good counselling [16][17][19][20][24][23][25], and regular follow ups [14][16] as being key facilitators in determining IPT adherence. Several studies have shown side effects [14][22][16][17][18][19][20][23][26], forgetfulness [16][17][19][20][24] , Distance to ART centre [16][19], and HIV related stigma [14][21][20][24] as key barriers for IPT adherence. Other barriers such as being busy [16][19] and weak medical provider relations[24] were also noted in some studies. Our study is also consistent with prior studies. Most of the facilitators and barriers are in concordance with earlier studies. In addition to that, quality of life was an important facilitator noted in our study. Side effects to IPT seemed to be the major barrier for adherence. Pill burden was also noted as one of the barriers. However, stigma did not seem to be a major barrier for IPT adherence in our study.

Significant variable found in univariate analysis was carried to multivariate and logistical regression analysis was done. Odds ratio with 95% confidence interval was generated. Participants who belonged to middle socioeconomic status had a 1.2 times higher likelihood to adherence than those from low socioeconomic status [AOR= 1.16; 95% CI: 0.332, 4.06]. Those who had good social support were 9 times more likely to adhere to IPT than the ones who lacked support [AOR= 8.77; 95% CI: 0.619, 125]. Participants who rated higher on visual analog scale were 11 times more likely to have good adherence than those who rated lower [AOR= 10.75; 95% CI: 2.63, 37.03] and statistical significance was noted (p <0.0001). Ones with prior history of TB were twice as likely to be adherent than those with no prior history [AOR= 2.08; 95% CI: 0.29, 14.92]. People with a higher CD4 count were 1.5 times more likely to be adherent than people with lower CD4 count [AOR=1.45; 95% CI: 0.43, 4.85].

Participants who had received advice from their physicians and felt it was useful were 7 times more likely to be adherent to IPT [AOR=7.329; 95% CI:0.532, 101.02]. Participants who had HIV duration longer than 10 years were 3 times more likely to be adherent than those below 10 years [AOR= 2.88; 95% CI: 0.294, 27.77]. Participants who found distance to ART centre impacting adherence had 96% lower odds of being adherent [AOR=0.042; 95% CI: 0.206, 2.28] and statistical significance was noted (p= 0.005). People who did not complain of pill burden were 6 times more likely to adhere to the desired course. [AOR=0.152; 95% CI: 0.011, 2.033]. List of facilitators and barriers noted in the study:

Facilitators	**Barriers**
Awareness about TB and IPT	Side effects
Good counselling on adherence	Distance to ART centre difficult
Regular follow ups	Forgetfulness
Physician advice to start IPT	Pill burden
Quality of life	
Social support	

Strengths of this study were that a standardised questionnaire was used to capture the relevant data. Also, adherence was assessed 6 months after the

completion of IPT as opposed to other studies which assessed adherence at much shorter intervals and time frames. On the other hand, some limitations of the study lie in that the Sample population was collected from ART centres attached to a single institution. Caregiver's knowledge, attitude and practices about IPT can also have an interplay with poor adherence. That was not assessed in this particular study.

Conclusion and Implications

High levels of adherence (83.75%) were noted in our study among PLHIV who received IPT. Facilitators noted in study were awareness about IPT and TB, good counselling, physician inputs, regular follow-ups, good quality of life and social support. Barriers noted were side effects to IPT, forgetfulness, pill burden and distance to ART centre. Identified barriers can be targeted and facilitators fortified upon to further strengthen the IPT adherence. The counselling efforts should be further strengthened and reiterated at every monthly follow up. Timely reminders to patients could be done wherever possible to overcome forgetfulness especially in PLHIV with dropping adherence. Regular follow ups and physician contact is key to good adherence rates. Dispensing more INH tablets to people who find distance to ART centre difficult for a monthly follow up may aid in overcoming this barrier. Addressing these situations can help with better adherence thereby leading to successful IPT implementation and mitigating the risk of TB and HIV.

Declaration of conflicting interests

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Consent

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