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Accumulation of HIV-1 Drug Resistance Mutations and Methamphetamine Use

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Abstract

Background: Antiretroviral therapy (ART) non-adherence and methamphetamine use are associated with higher HIV drug resistance prevalence. How they affect drug resistance mutations accumulation is less studied.

Objective: We assessed factors associated with drug resistance mutations accumulation.

Methods: We evaluated HIV chronically-infected patients from a clinic-based research cohort on first-line ART regimens with genotype results within 30 days of baseline. Methamphetamine use and ART adherence were self-reported at each study visit. High ART adherence was defined as 0–5% missed doses in the prior 30 days.

Results: One-hundred twenty-five patients contributed 496 study visits. At baseline, 81% of patients reported high ART adherence; 90% reported no methamphetamine use in the prior 4 months, 8% used monthly or less and 2% used daily or weekly. Methamphetamine users and non-users had similarly high ART adherence (p=0.93). Adjusted incidence rate ratio (aIRR) of drug resistance mutations accumulation was 2.04 (95% CI 0.64, 6.46) for daily/weekly users and 1.71 (95% CI 0.66, 4.42) for patients with monthly or less users, compared to non-users. aIRR was 0.71 (95% CI 0.44, 1.15) with >5–10% missed ART doses and 1.21 (95% CI 0.80, 1.83) with >10% missed doses compared to 0–5% missed doses.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE:
Approval of this study was obtained from the Institutional Review Board (Approval no. 10–01330) at the University of California San Francisco.

HUMAN AND ANIMAL RIGHTS:
No animals were used in this research. All human research procedures were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2013.

CONSENT FOR PUBLICATION:
The studied participants were informed about the present research, and a written consent form was taken from all of them before their enrollment.

STANDARD OF REPORTING:
This study conforms to the research guidelines of the Institutional Review Board at the University of California San Francisco.

CONFLICT OF INTEREST:
The authors declare no conflict of interest, financial or otherwise.

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Conclusions: We found no strong evidence for an effect of methamphetamine use and ART adherence on drug resistance mutations accumulation. Research cohort patients may have been more engaged in care and treatment adherent than non-cohort patients. Our findings suggest methamphetamine use might not lead to treatment failure among HIV patients who are otherwise engaged in care.

Keywords

HIV; drug resistance; mutations; antiretroviral therapy; treatment adherence; methamphetamines

INTRODUCTION

Methamphetamine use is prevalent among persons living with HIV. In a nationally representative sample of persons diagnosed with HIV between 2015 and 2016 in the US, 9.6% of HIV-positive men who have sex with men (MSM) reported amphetamine use in the past 12 months [1]. An annual web-based behavioral survey of MSM living in the US conducted between 2013 and 2017 found methamphetamine use among HIV-positive MSM ranged from 10.4% to 12.9% compared to 1.9% to 2.4% among HIV-negative MSM [2]. Methamphetamine use among HIV-positive MSM in other studies ranged from 6% to 28%, varying by study location and year [3–5].

Methamphetamine use has been associated with non-adherence to antiretroviral therapy (ART) [6–8]. A longitudinal study found HIV-positive persons who were stimulant users (e.g., cocaine, methamphetamine) were seven times more likely to have poor ART adherence [9]. HIV-positive MSM participating in a qualitative study noted methamphetamine use had a negative impact on their ability to adhere to their ART regimen [10]. Viral suppression was found to be less complete among HIV-positive persons who use methamphetamine [11,12].

Methamphetamine use has been associated with a higher prevalence of HIV-1 drug resistance [13–16]. Frequent methamphetamine use was associated with transmitted drug resistance (TDR) to any class of HIV drugs, particularly non-nucleoside transcriptase inhibitors [14,15]. Among newly-diagnosed HIV cases at a municipal sexually transmitted infections (STI) clinic, 25% of persons with TDR had a history of methamphetamine use [17].

Whether methamphetamine use affects the accumulation of HIV-1 drug resistance mutations has been less studied. We assessed factors associated with the accumulation of drug resistance mutations over time in a prospective clinic-based research cohort of patients with chronic HIV infection.

MATERIALS & METHODS

We conducted a secondary analysis of data from the Study of the Consequences of the Protease Inhibitor Era (SCOPE), a prospective clinic-based research cohort of patients with chronic HIV infection at the University of California, San Francisco. The large clinical dataset contains clinical information such as ART regimen, viral load and viral genotype [18]. Patients included in this analysis had their baseline visit during 2000 to 2003, had a

viral genotype result within 30 days of their baseline visit, were stable on their first ART regimen, and had two or more genotype results, with at least one prior to and one during their first ART regimen.

Patients completed surveys every four months for the duration of their enrollment in the study. Demographic characteristics assessed included gender, age, race/ethnicity, sexual orientation and education. Self-reported measures collected at each study visit included HIV transmission risk, number of male sex partners, substance use and ART adherence. Clinical characteristics evaluated included years since HIV diagnosis, ART regimen, viral load and presence of drug-resistant mutations.

The primary outcome of interest was the accumulation of HIV-1 drug resistance mutations at each study visit. Viral population sequencing of plasma viral RNA generated the full protease and portions of the reverse transcriptase reading frames (TRUGENE HIV-1 Genotyping Assay). Sequencing results were interpreted using guidelines from the manufacturer, IAS-USA, and the Stanford University HIV-1 Drug Resistance Surveillance Program.[19,20] Accumulation of drug resistance mutations at follow-up was defined as the difference in total resistance mutations at the follow-up visit compared to the baseline visit.

Frequency distributions were calculated for categorical variables. Medians and interquartile ranges (IQR) were calculated for continuous variables. Bivariate and multivariable generalized estimating equations (GEE) were used to examine associations with drug resistance mutation accumulation, accounting for multiple observations per participant; the negative binomial link, robust standard errors, and exchangeable working correlations were used. The primary predictor of interest was methamphetamine use in the four months preceding a study visit. Methamphetamine use was categorized as daily or weekly, monthly or less, and no use. ART adherence was categorized based on the percentage of missed doses in the 30 days prior to a study visit: 0–5% missed doses (“high” adherence), >5–10% missed doses or >10% missed doses. Statistical analysis was performed using STATA Statistical Software: Release 14 (StataCorp LP, College Station, TX).

RESULTS

One-hundred twenty-five patients contributed a total of 496 study visits to this analysis; 125 were baseline visits and 271 were follow-up visits. The median number of observations included per patient was 3 (IQR: 2–5). Table 1 presents patients’ demographic characteristics and risk behaviors at baseline. The majority of patients were male (82.4%) and self-identified as gay (62.4%); 46.4% of patients were white. At baseline, the median age was 46 years (IQR: 40–51) and the median time since HIV diagnosis was 11 years (IQR: 8–14). Patients’ primary HIV transmission risk was sex with men (76.8%), with a smaller proportion attributing their acquisition risk to injection drug use (19.2%) and sex with women (14.4%). Patients reported a median of 1 male sex partner in the past four months (IQR: 0–2).

Thirteen patients (10.4%) reported using methamphetamines in the four months prior to the baseline visit, the majority of whom used on a monthly or less basis. Ninety patients

(81.1%) reported 0–5% missed doses of ART in the 30 days prior to the baseline study visit. Methamphetamine users (n=8 of 10) and non-users (n=82 of 101) had similarly high ART adherence (p=0.93). The median viral load at baseline was 6,811 copies per milliliter (IQR: 1,054, 25,379).

At the baseline visit, 112 patients (89.6%) were on their first-line ART regimen and 13 patients were treatment-naïve (10.4%). All treated patients were on a first-line regimen that included nucleoside reverse transcriptase inhibitors (NRTIs). Eighty-five patients were on dual-class therapy, including 67 patients on NRTIs + protease inhibitors (PIs) regimens and 17 patients on NRTIs + non-nucleoside reverse transcriptase inhibitors (NNRTIs) regimens. Sixteen patients were on a triple-class therapy regimen of NRTIs + NNRTIs + PIs.

Patients had a median of 3 visits (range 2–5 visits) with genotyping data available. The median number of drug resistance mutations at baseline was 5 (IQR: 2–8). The majority of mutations detected at baseline conferred resistance to NRTIs, the most common being M184V (n=77), M41L (n=48), T215Y (n=42), D67N (n=33) and L210W (N=28). The most common mutations conferring resistance to NNRTIs were K103N (n=40), G190A (n=13) and Y181C (n=10). The most common mutations conferring resistance to PIs were L90M (n=42), I54V (N=30), M46I (n=28) and V82A (n=28).

Four of the 13 treatment-naïve patients had drug resistance mutations detected at baseline, yielding an overall TDR prevalence of 30.8%. Three patients had mutations conferring resistance to NRTIs, for a 23.1% TDR prevalence. One patient carried the M41L and T215D mutations, another patient carried the K219K/Q mutation, and the third patient carried the T215D mutation. One patient carried the K103N mutation which conferred resistance to NNRTIs. Four treatment-naïve patients reported methamphetamine use, including one with TDR who reported monthly or less frequency of use. Methamphetamine use was not associated with TDR (p=0.91).

The overall incidence rate of HIV-1 drug resistance mutation accumulation was 0.62 mutations per year. Stratified by methamphetamine use in the four months prior to baseline, the incidence rate was 0.58 mutations per year for patients reporting no use and 0.98 for patients reporting any use. Bivariate and multivariable GEE models assessing factors associated with the accumulation of drug resistance mutations are shown in Table 2. In bivariate analysis, the incidence rate ratio (IRR) of mutation accumulation was 1.93 (95% confidence interval (CI): 0.57, 6.56) for patients reporting daily or weekly methamphetamine use and 1.49 (95% CI: 0.61, 3.62) for those with monthly or less use, compared to patients who reported no use in the four months prior to that study visit. In multivariable analysis, the adjusted IRR (aIRR) of drug resistance mutation accumulation was 2.04 (95% CI: 0.64, 6.46) for patients with daily or weekly methamphetamine use and 1.71 (95% CI: 0.66, 4.42) for patients with monthly or less use, compared to non-users in the four months prior to that study visit. The aIRR was 0.71 (95% CI: 0.44, 1.15) for patients with >5–10% missed ART doses in the past 30 days and 1.21 (95% CI: 0.80, 1.83) for those with >10% missed doses, compared to patients with 0–5% missed doses. Time since HIV diagnosis (p=0.08) and age (p=0.57) were not associated with the accumulation of drug resistance mutations.

DISCUSSION

We found no strong evidence for an effect of methamphetamine use and ART adherence on the accumulation of HIV-1 drug resistance mutations. There was a marginal increase in risk of acquiring drug resistance mutation among patients who reported methamphetamine use and patients who reported missing >10% of ART doses. High adherence levels overall in our study population may account in part for the lack of a significant association observed. Treatment adherence was comparable between methamphetamine users and non-users in our cohort. The 80% ART adherence reported by the methamphetamine users in our patient cohort was similar to the levels found in other studies [21–23]

Methamphetamine use at baseline was 10.4% in our cohort, which was similar to the 9.6% among HIV-positive men in the national Medical Monitoring Project and the 11.5% among participants in the American Men's Internet Survey [1,2]. However, methamphetamine use in our cohort was lower than levels reported in San Francisco community surveys, which ranged from 20% to 28% among HIV-positive men [4,5]. The same community surveys also found methamphetamine use ranged from 9% to 14% among HIV-negative men [4,5].

Nearly one-third of treatment-naïve patients had TDR mutations. The 23.1% prevalence of NRTI TDR was similar to the 20.9% reported in a case series of recently-infected patients in San Francisco around the same time period [24]. We did not observe an association between methamphetamine use and TDR, which is similar to the study findings among persons newly-diagnosed with HIV at the municipal sexually transmitted disease clinic in San Francisco [17]. Our study sample had a small number of treatment-naïve patients since examining an association between methamphetamine use and TDR was not the primary intent of this analysis. A larger sample of treatment-naïve patients might have yielded results more similar to other studies that reported a correlation [14,15,17].

The main limitations of our analysis were the small cohort size and the few patients who reported methamphetamine use and ART non-adherence. Patients might have under-reported their methamphetamine use and users might have been more likely to over-report their ART adherence compared to non-users. Self-reported data for these measures, however, have been used in prior studies [1–8,13–17,21–25]. Our patients may have been more engaged in care and more adherent to therapy than other HIV patients who were not part of the research study cohort. Patients included in this analysis may differ from the other SCOPE patients who were excluded because they did not meet the inclusion criteria. Lastly, these results may not reflect current patient experiences as treatment options have vastly improved. However, our study offers a methodological approach to track the accumulation of HIV-1 drug resistance mutations over time, with these findings providing a baseline for comparison for future studies.

CONCLUSION

Our findings suggest that methamphetamine use might not lead to treatment failure among HIV patients who are otherwise engaged in care and are treatment adherent. Though some methamphetamine users may struggle with ART adherence more than non-users,

interventions that support and bolster overall engagement in HIV care can greatly benefit these individuals. The current treatment landscape offers ART formulations with improved efficacy and simpler dosing schedules, which can facilitate adherence and decrease the risk of acquiring drug resistance. Our findings highlight the importance of retaining patients in care to achieve viral suppression and prevent the accumulation of HIV-1 drug resistance mutations.

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AVAILABILITY OF DATA AND MATERIAL:

The authors confirm that the data supporting the results and findings of this study are available within this article.

REFERENCES

1. Maloney KM, Beer L, Tie Y, Dasgupta S. Prevalence of non-medical amphetamine use among men with diagnosed HIV infection who have sex with men in the United States, 2015–2016. AIDS Behav. 2020;24:1865–75.
2. Sanchez TH, Zlotorzynska M, Sineath RC, Kahle E, Tregear S, Sullivan PS. National trends in sexual behavior, substance use and HIV testing among United States men who have sex with men recruited online, 2013 through 2017. AIDS Behav. 2018;22:2413–25.
3. Zlotorzynska M, Canta C, Rai R, Sullivan P, Sanchez T. The annual American Men's Internet Survey of men who have sex with men in the United States: 2017 key indicators report. JMIR Public Health Surveill. 2020;6:e16847.
4. Schwarcz S, Scheer S, McFarland W, et al. Prevalence of HIV infection and predictors of high-transmission sexual risk behaviors among men who have sex with men. Am J Public Health. 2007;97:1067–75.
5. Vaudry J, Raymond HF, Chen S, Hecht J, Ahrens K, McFarland W. Indicators of use of methamphetamine and other substances among men who have sex with men, San Francisco, 2003–2006. Drug Alcohol Depend. 2007;90:97–100.
6. Marquez C, Mitchell SJ, Hare CB, John M, Klausner JD. Methamphetamine use, sexual activity, patient-provider communication, and medication adherence among HIV-infected patients in care, San Francisco, 2004–2006. AIDS Care. 2009;21:575–82.
7. Gonzalez A, Barinas J, O'Cleirigh C. Substance use: impact on adherence and HIV medical treatment. Curr HIV/AIDS Rep. 2011;8:223–34.
8. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. Amer J Med. 2003;114:573–80.
9. Hinkin CH, Barclay TR, Castellon SA, et al. Drug use and medication adherence among HIV-1 infected individuals. AIDS Behav. 2007;11:185–94.
10. Reback CJ, Larkins S, Shoptaw S. Methamphetamine abuse as a barrier to HIV medication adherence among gay and bisexual men. AIDS Care. 2003;15:775–85.
11. Ellis RJ, Childers ME, Cherner M, et al. Increased human immunodeficiency virus loads n active methamphetamine users are explained by reduced effectiveness of antiretroviral therapy. J Infect Dis. 2003;188:1820–6.

12. Carrico AW, Hunt PW, Neilands TB, et al. Stimulant use and viral suppression in the era of universal antiretroviral therapy. J Acquir Immune Defic Syndr. 2019;80:89–93.
13. Rajasingham R, Mimiaga MJ, White JM, Pinkston MM, Baden RP, Mitty JA. A systematic review of behavioral and treatment outcome studies among HIV-infected men who have sex with men who abuse crystal methamphetamine. AIDS Patient Care STDs. 2012;26:36–52.
14. Cachay ER, Moini N, Kosakovsky, et al. Active methamphetamine use is associated with transmitted drug resistance to non-nucleoside reverse transcriptase inhibitors in individuals with HIV infection of unknown duration. Open AIDS J. 2007;1:5–10.
15. Colfax GN, Vittinghoff E, Grant R, Lum P, Spotts G, Hecht FM. Frequent methamphetamine use is associated with primary non-nucleoside reverse transcriptase inhibitor resistance. AIDS. 2007;21:239–41.
16. Gorbach PM, Drumright LN, Javanbakht M, et al. Antiretroviral drug resistance and risk behavior among recently HIV-infected men who have sex with men. J Acquir Immune Defic Syndr. 2008;47:639–43.
17. Truong HM, Kellogg T, McFarland W, et al. Sentinel surveillance of HIV-1 transmitted drug resistance, acute infection and recent infection. PLoS One. 2011;6:e25281.
18. Deeks SG, Hecht FM, Swanson M, et al. Virologic outcomes with protease inhibitor therapy in an urban AIDS clinic: relationship between baseline characteristics and response to both initial and salvage therapy. AIDS. 1999;13:F35–43.
19. International Antiviral Society-USA. HIV drug resistance mutations. Available at: https://www.iasusa.org/content/drug-resistance-mutations-in-HIV.
20. HIV-1 Drug Resistance Surveillance Program. Available at: http//hivdb.stanford.edu.
21. Carrico AW, Riley ED, Johnson MO, et al. Psychiatric risk factors for HIV disease progression: the role of inconsistent patterns of antiretroviral therapy utilization. J Acquir Immune Defic Syndr. 2011;56:146–50.
22. Moore DJ, Blackstone K, Woods SP, et al. Methamphetamine use and neuropsychiatric factors are associated with antiretroviral non-adherence. AIDS Care. 2012;24:1504–13.
23. Parsons JT, Kowalczyk WJ, Botsko M, Tomassilli J, Golub SA. Aggregate versus day level association between methamphetamine use and HIV medication non-adherence among gay and bisexual men. AIDS Behav. 2013;18:1478–87.
24. Grant RM, Hecht FM, Warmerdam M, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. JAMA. 2002;288:181–8.
25. Truong HM, Grant RM, McFarland W, et al. Routine surveillance for the detection of acute and recent HIV infections and transmission of drug resistance. AIDS. 2006;20:2193–7.

Table 1

Demographic, behavioral and clinical characteristics at baseline study visit, SCOPE patients (n=125)

	n (%) or median (IQR)
Demographic Characteristics	
Gender	
Male	103 (82.4)
Female	19 (15.2)
Transgender (male-to-female)	3 (2.4)
Age	46 (40–51)
25–34	11 (8.8)
35–44	45 (36.0)
45–54	48 (38.4)
≥55	21 (16.8)
Race	
White	58 (46.4)
Black	40 (32.0)
Hispanic/Latino	14 (11.2)
Asian	3 (2.4)
Mixed	10 (8.0)
Sexual orientation	
Gay/Men who have sex with men	78 (62.4)
Heterosexual	36 (28.8)
Bisexual	11 (8.8)
Education (highest level completed)	
GED/Graduated high school, or less	45 (36.0)
Some college/associates degree	45 (36.0)
4-year college degree	22 (17.6)
Attended/completed grad school	13 (10.4)
Behavioral Characteristics	
How do you think you first got infected with HIV? (not mutually exclusive)	
From sex with men	96 (76.8)
From sex with women	18 (14.4)
From sharing injection needles	24 (19.2)
Other reason	6 (4.8)
Number of male partners (past 4 months)	
0	60 (48.4)
1	30 (24.2)
>1	34 (27.4)
Injection drug use (past 4 months)	
No	113 (90.4)
Yes	12 (9.6)

	n (%) or median (IQR)
Methamphetamine use (past 4 months)	
Never	112 (89.6)
Monthly or less	10 (8.0)
Daily/weekly	3 (2.4)
Clinical Characteristics	
Years since diagnosis	11 (8–14)
0–5	16 (13.0)
6–10	40 (32.5)
11–15	50 (40.7)
>15	17 (13.8)
Viral load (copies/ml)	6,811 (1,054–25,379)
≤ 400	16 (12.8)
401–1,000	15 (12.0)
1,001–10,000	45 (36.0)
10,001–100,000	42 (33.6)
>100,000	7 (5.6)
ART regimen (drug class)	
NRTI + NNRTI + PI	16 (12.8)
NRTI + PI	67 (53.6)
NRTI + NNRTI	17 (13.6)
NRTI	8 (6.4)
NRTI + PI + FI	3 (2.4)
NRTI + FI	1 (0.8)
None	13 (10.4)
% ARV missed doses (past 30 days)	
0–5%	90 (81.1)
>5–10%	14 (12.6)
>10%	7 (6.3)
Number of genotyping mutations at baseline	5 (2–8)
Number of visits with genotyping data	3 (2–5)

Table 2

Bivariate and multivariable associations with accumulation of HIV-1 drug resistant mutations, adjusted for multiple observations per person (n=125 patients, n=496 observations)

	Bivariate		Multivariable	
Demographic Characteristics	**IRR (95% CI)[α]**	**p-value**	**aIRR (95% CI)[β]**	**p-value**
Gender				
Male	ref *		-	
Female	1.01 (0.54, 1.87)	0.78	-	
Transgender (male-to-female)	0.65 (0.20, 2.16)		-	
Age				
25–34	ref		ref	
35–44	2.15 (0.95, 4.86)	0.17	1.29 (0.53, 3.16)	0.57
45–54	1.70 (0.76, 3.84)		1.28 (0.53, 3.12)	
≥ 55	2.74 (1.06, 7.11)		2.32 (0.67, 8.04)	
Sexual orientation				
Gay/ Men who have sex with men	ref		-	
Heterosexual	0.89 (0.51, 1.52)	0.73	-	
Bisexual	1.44 (0.43, 4.83)		-	
Race				
White	ref		-	
Black	1.14 (0.62, 2.11)		-	
Hispanic/Latino	1.23 (0.64, 2.37)	0.58	-	
Asian	1.79 (0.60, 5.37)		-	
Mixed	0.44 (0.10, 1.97)		-	
Education (highest level completed)				
GED/high school or less	ref		-	
Some college/associates degree	1.33 (0.74, 2.39)	0.62	-	
4-year college degree	1.44 (0.72, 2.81)		-	
Attended/completed grad school	1.71 (0.57, 5.17)		-	
Behavioral Characteristics				
Number of male partners (past 4 months)				
0	ref		-	
1	0.90 (0.47, 1.73)	0.79	-	
>1	1.09 (0.62, 1.91)		-	
Injection drug use (past 4 months)				
No	ref		-	
Yes	0.82 (0.16, 4.23)	0.82	-	
Methamphetamine use (past 4 months)				
Never	ref		ref	
Monthly or less	1.49 (0.61, 3.62)	0.56	1.71 (0.66, 4.42)	0.45
Daily/weekly	1.93 (0.57, 6.56)		2.04 (0.64, 6.46)	

	Bivariate		Multivariable	
Demographic Characteristics	**IRR (95% CI)[α]**	**p-value**	**aIRR (95% CI)[β]**	**p-value**
Clinical Characteristics	**IRR (95% CI)[α]**	**p-value**	**aIRR (95% CI)[β]**	**p-value**
Years since diagnosis at this visit (per 1 year)	1.07 (1.02, 1.13)	<0.01	1.05 (0.99, 1.12)	0.08
Viral load at this visit (copies/ml)				
≤ 400	ref		-	
401–1000	0.41 (0.17, 0.96)		-	
1001–10,000	0.66 (0.32, 1.36)	0.30	-	
10,001–100,000	0.83 (0.37, 1.84)		-	
>100,000	0.68 (0.24, 1.90)		-	
% ARV missed doses (past 30 days)				
0–5%	ref		ref	
> 5–10%	0.66 (0.39, 1.14)	0.12	0.71 (0.44, 1.15)	0.11
> 10%	1.16 (0.74, 1.81)		1.21 (0.80, 1.83)	

[α] IRR: incidence rate ratio; 95% CI: 95% confidence interval

[β] aIRR: adjusted incidence rate ratio

[*] ref: reference category