

# Survival and associated factors among people living with HIV/AIDS: A 30-year national survey in Iran

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**Background:** The survival in Iranian HIV/AIDS patients based on data from Iran National HIV/AIDS Case Registry System has not been evaluated. This study assessed the survival rates and associated factors among people living with HIV/AIDS in Iran. **Materials and Methods:** The population in this observational study included 32168 patients diagnosed with HIV/AIDS registered in Iran disease registry system between 1986 and 31 December 2015. Data until June 2016 (the cutoff date of our last data linkage) were investigated to estimate survival and related factors following HIV diagnosis. **Results:** Of registered patients, 17.7% were diagnosed at AIDS stage. By June 2016, 27.2% of study population progressed to AIDS, and 8081 (25.1%) of patients died. The survival rate was 88%, 85%, 77%, and 67% for 1, 2, 5, and 10 years, respectively. Cumulative proportion surviving was significantly lower in males than in females ( $P = 0.0001$ ). A higher rate of survival was seen in female patients, who diagnosed after 2010, infected in sexual route, and had CD4 cell count more than 500, nonconfected patients with tuberculosis (TB), and those who received antiretroviral therapy (ART). Based on multivariate model, the mortality risk in female patients, those with CD4 cell count more than 500, patients who received ART, and those with TB and injection drug uses (IDUs) was higher. **Conclusion:** The survival in studied patients increased in recent time periods, and ART reduced AIDS-related mortality in these patients. The survival can be increased by focus on improvements in patient care among male patients, IDUs, and patients with TB coinfection.

**Key words:** Antiretroviral therapy, HIV/AIDS, Iran, survival

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## INTRODUCTION

Worldwide, despite widespread efforts to control the disease, HIV/AIDS remains a serious public health challenge.<sup>[1]</sup> Based on the UNAIDS global estimation, by the end of 2016, there were 36.7 million people living with HIV, 1.0 million deaths from AIDS-related causes, and 1.8 million new HIV infections.<sup>[2]</sup>

Since the introduction of antiretroviral therapy (ART), AIDS-defining opportunistic infections and AIDS-related mortalities were decreased, and long-term survival in HIV-positive populations appears to be approaching

that of the general population.<sup>[3]</sup> Studies have shown declining rates of AIDS-related death compared to non-AIDS-related death.<sup>[4,5]</sup> and describe a need for increasing focus on chronic disease management and health promotion.<sup>[6,7]</sup> This effective treatment increases survival following HIV infection from 10 to 12 years to 25 years,<sup>[8,9]</sup> and HIV infection can now be characterized as a manageable chronic condition.<sup>[10]</sup>

The accurate description of survival in HIV-positive populations today is therefore increasingly important in HIV management. The effectiveness of ART varies between countries.<sup>[11,12]</sup> However, most of the previous studies have shown that ART significantly reduced the

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rate of disease progression from HIV to death, but in some other studies, the discrepancy is reported in the survival rates of patients with HIV infection.<sup>[13,14]</sup>

Reporting treatment outcomes of patients enrolled in ART programs is important to demonstrate program effectiveness and justify continued funding that can help to identify opportunities for program improvement.<sup>[15]</sup> Few studies have reported survival in HIV patients in Iran, and there are no studies describing survival in total of Iranian people who lived with HIV/ADS. Therefore, the aim of the present study was to assess the 1-, 2-, 5-, and 10-year survival rate among people living with HIV/ADS based on Iran HIV/AIDS Surveillance Registry and clarify the determinants of survival rate in these patients.

## MATERIALS AND METHODS

### Study design and participants

This is an observational survival analysis, based on data from the Iran National HIV/AIDS Case Registry System, Centre of Communicable Disease Control, Ministry of Health and Medical Education. The study population included all patients ( $n = 32168$ ) who were diagnosed and registered with HIV/AIDS in Iran between 1986 (the first diagnosed case of HIV) and 31 December 2015. The registry includes all demographic, laboratory, pharmacy, outpatient clinic visit, as well as dates of death. Data from these individuals until June 2016 (the cutoff date of our last data linkage) were investigated to estimate survival and related factors following HIV diagnosis. The study protocol was approved by the Institutional Review Board and Ethical Committee of Shiraz University of Medical Sciences (no, 11382-95).

### Study variables

The demographic and clinical characteristics used in this study included; number of HIV/AIDS cases, date of HIV diagnosis (the date of positive test), age at diagnosis (patients years old at diagnosis time), gender (male and female), baseline CD4 count (cell/mm<sup>3</sup>), disease stage (HIV infection or AIDS stage), date of progression to AIDS, number of AIDS-related deaths, date of death, tuberculosis (TB) confection status, ART (the status of receive treatment in last visit), and route of transmission (injection drug use [IDU], sexual route, and blood transfusion other route). The time to event in months was the primary outcome in this study, and the time between the dates of HIV diagnosis and the date death or date of censoring was used to calculate the survival time in months.

### Statistical analyses

Statistical analyses were done using SPSS software for Windows (SPSS, Inc., version 24, Chicago, IL, USA). Descriptive data are reported as mean  $\pm$  standard deviation, mean (95% confidence interval [CI]) for length of

life from diagnosis to death, median (interquartile range) for survival time, and number (percent) for categorical data. Chi-square test was used to assess the frequency of the disease between age groups, genders, disease stage, ART status, TB confection status, CD4 count, and route of transmission. Length of life from diagnosis to death was compared in the levels of other factors using Kruskal–Wallis test. Survival time was considered as the interval from the date of HIV/AIDS diagnosis to the date of death and was expressed in months. The Kaplan–Meier method was used to estimate cumulative survival probability, and comparisons between survival curves were performed with the log-rank test. The Cox proportional hazards regression model was applied to examine association between overall survival and the main factors. All statistical tests were two-sided and  $P < 0.05$  was considered to be statistically significant.

## RESULTS

Based on data from the national HIV/AIDS surveillance system, a total of 32168 HIV-infected patients had been identified and registered in Iran. The mean age of patients at diagnosis was  $33.2 \pm 9.6$  years (range; newborn - 91 years). Majority of those (84.3%) were male and 15.7% were female. At the time of diagnosis, 17.7% of study population were at the AIDS stage. Progression rate to AIDS in the whole population was 27.2% (8756 patients) until the end of the follow-up period. Based on Chi-square test, the frequency of the disease progression was significantly different between both genders (26% and 45% for men and women, respectively;  $P < 0.0001$ ).

By June 2016, 8081 of the 32168 (25.1%) registered cases died. The survival rate for whole population was 88%, 85%, 77%, and 67% for 1, 2, 5, and 10 years, respectively. Cumulative proportion surviving was remarkably lower in males than in females (1-, 2-, 5-, and 10-year survival rate was 87%, 83%, 75%, and 65% among men in comparison with 94%, 93%, 89%, and 83% among women, based on log-rank test).

Table 1 describes the analyses of the risk factors for death in the studied population. Age and sex were found to be risk factors with higher mortality within older patients and the male gender. The rate of mortality in HIV patients infected with TB and those with baseline CD4 count lower than 500 was higher. ART was a protective factor with lower mortality within patients who received ART. Furthermore, mortality rate in infected patients by blood transfusion routes or in IDUs was significantly higher than the other patients.

Figure 1 shows the Kaplan–Meier survival curves of all the patients and according to the mode of transmission and era of HIV diagnosis. A higher rate of survival was seen in

**Table 1: Risk factors associated with mortality in human immunodeficiency virus-positive individuals**

Characteristics	Frequency	Death*	Length of life from diagnosis to death (month) <sup>†</sup>	Survival time (month) <sup>††</sup>
Overall	32,168	7733 (25.7)	27 (6-62)	248.0 (244.3-251.7)
Age at diagnosis (year)				
≤15	648 (2.39)	102 (15.7)	30.1 (23.2-37.0)	253.7 (235.7-271.7)
16-30	10,747 (39.67)	2760 (25.7)	46.9 (45.4-48.5)	215.2 (211.5-219.0)
31-45	13,613 (50.25)	3934 (28.9)	37.6 (36.4-38.8)	196.0 (192.7-199.3)
46-60	2509 (9.26)	781 (31.1)	26.9 (24.6-29.3)	166.3 (160.4-172.1)
61+	220 (0.81)	72 (32.7)	16.9 (10.3-23.5)	143.6 (127.1-160.1)
Gender				
Male	27,130 (84.34)	7537 (27.8)	39.9 (39.0-40.8)	240.8 (236.8-244.9)
Female	5038 (15.66)	530 (10.5)	33.0 (29.6-36.3)	256.9 (249.5-264.3)
Baseline CD4 count (cell/mm <sup>3</sup> )				
<500	9801 (73.12)	1964 (20.0)	54.5 (52.5-56.4)	214.5 (207.6-221.5)
≥500	3603 (26.88)	430 (11.9)	64.6 (60.7-68.4)	216.5 (210.1-222.8)
TB status				
Coinfection	1028 (3.20)	450 (43.8)	56.0 (52.0-60.1)	122.3 (115.8-128.9)
No TB	31,140 (96.80)	7617 (24.5)	38.7 (37.8-39.6)	251.6 (247.9-255.3)
ART status				
ART treatment	9697 (32.24)	1466 (15.1)	55.1 (52.7-57.5)	223.7 (214.1-233.3)
No treatment	20,380 (67.76)	6266 (30.7)	36.0 (35.1-36.9)	243.2 (240.5-245.9)
Disease status				
HIV infection	23,412 (72.78)	6556 (28.0)	36.8 (35.9-37.7)	242.5 (238.5-246.6)
Progression to AIDS	8756 (27.22)	1511 (17.3)	52.0 (49.8-54.3)	225.1 (217.2-233.1)
MOT				
Injection drug use	20,240 (69.02)	6383 (31.5)	40.3 (39.3-41.2)	237.1 (234.1-240.1)
Sexual route	6047 (20.62)	774 (12.8)	38.5 (35.4-41.5)	239.6 (230.8-248.4)
Blood transfusion	138 (0.47)	79 (57.2)	50.5 (40.5-60.5)	167.1 (142.9-191.4)
Mother to child	498 (1.70)	72 (14.5)	26.4 (18.2-34.6)	162.6 (151.1-174.1)
Others	2401 (8.19)	421 (17.5)	32.9 (28.9-36.9)	203.5 (197.8-209.2)
Era of HIV diagnosis				
Before 1999	1550 (5.12)	648 (41.8)	72.4 (68.4-76.5)	242.6 (234.8-250.5)
2000-2009	17,394 (57.48)	5723 (32.9)	42.9 (41.9-43.9)	143.1 (141.9-144.3)
≥2010	11317 (37.40)	1544 (13.6)	13.9 (13.0-14.8)	66.8 (66.3-67.3)

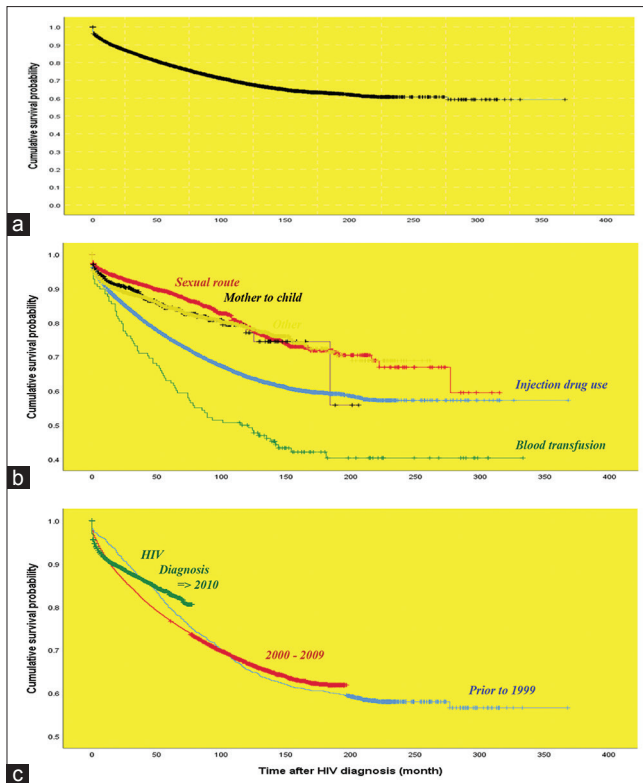
All data except as noted are reported as number, *n* (%), Mean (95% CI) and Median (IQR). In some cases, numbers do not add up to totals because of missing values.

\**P* values calculated by Chi-square test, all *P*<0.05, †*P* values calculated by Kruskal-Wallis test, all *P*<0.05, ††*P* values calculated by log-rank test, all *P*<0.05. AIDS=Acquired immunodeficiency syndrome; CI=Confidence interval; ART=Antiretroviral therapy; MOT=Mode of transmission; TB=Tuberculosis; HIV=Human immunodeficiency virus; IQR=Interquartile range

patients infected in sexual route, and lower rate of survival was seen in IDUs and patients infected in blood transfusion route (*P* = 0.0001). Furthermore, the rate of survival in patients diagnosed after 2010 was significantly higher than those patients who were diagnosed between 2000 and 2009 or before 1999 (*P* = 0.0001).

Figure 2 shows the survival analysis of studied patients according to sex, age group, CD4 cell count, ART, the presence of TB, and AIDS status. The rate of survival among females was significantly more than males. Patients in older age group had lower rate of survival than younger patients. Survival rate in patients with CD4 cell count more than 500 was significantly higher than patients with CD4 cell count lower than 500. Patients who received ART had significantly better survival than those patients that did not received ART. Furthermore, the survival rate among confected patients by TB was significantly more than nonconfected patients.

All the studied variables were statistically significant in univariate and therefore were entered in multivariable analyses. Table 2 shows the results for multivariable associations between mortality hazard and sex, age at diagnosis, CD4 cell count, AIDS diagnosis, ART, the presence of TB, and mode of transmission. The multivariate model shows a decreasing in the mortality risk in female patients (hazard ratio [HR], 0.701; 95% CI, 0.627–0.784), those with CD4 cell count more than 500 (HR, 0.046; 95% CI, 0.395–0.481), and patients who received ART (HR, 0.541; 95% CI, 0.501–0.585). In contrast, older patients at diagnosis time (HR, 1.019; 95% CI, 1.016–1.021) and those with TB (2.056; 95% CI, 1.860–2.272) were at risk of death. Furthermore, the risk of mortality in patients who infected in sexual mode was lower than IDUs, whereas mortality risk by mother-to-child mode as of transmission was increased compared to IDUs (HR, 1.699; 95% CI, 1.325–2.178).



**Figure 1:** Kaplan–Meier product limits estimates for probability of survival (a) overall, (b) stratified by mode of transmission, and (c) stratified by era of HIV diagnosis

## DISCUSSION

The present study estimated the survival rate of patients with HIV/AIDS at several time intervals and related risk factors based on Iran's HIV registry system. Although like many other national surveillance systems, surveillance of communicable diseases, including AIDS, in Iran suffers from quality,<sup>[16]</sup> our results showed that from the beginning of the presence of HIV/AIDS in Iran, nearly one in four patients died, with the mean survival time of 248 months for all HIV/AIDS patients. The mortality decreased between 2000 and 2009, after the introduction of monotherapy regimens, in comparison to before 1999 period. Furthermore, after the introduction of triple therapy, mortality in HIV/AIDS patients was decreased after 2010 compared to 2000–2009 period. These findings are similar to other studies that have reported similar results in developed countries. These studies in France, Canada, Switzerland, and the United States have reported reducing mortality after the introduction of triple therapy; however, the decreased in mortality rate in these countries was higher than in our country and was occurred very sooner.<sup>[17-20]</sup> The poor ART program initiatives and low coverage of the program in Iran can explain the differences between our findings with studies in developed countries. Furthermore, studies in Asia and South Africa have shown similar results in mortality

**Table 2: Multivariate analysis of the baseline factors associated with mortality among human immunodeficiency virus-positive individuals**

Characteristics	HR	95.0% CI	P
Sex (reference; male)	0.701	0.627-0.784	<0.0001
Age at diagnosis	1.019	1.016-1.021	<0.0001
CD4 count (ref; <500)	0.436	0.395-0.481	<0.0001
AIDS (reference; HIV infection)	0.823	0.760-0.890	<0.0001
Antiretroviral therapy	0.541	0.501-0.585	<0.0001
TB	2.056	1.860-2.272	<0.0001
Mode of transmission (reference; IDU)			
Sexual	0.664	0.605-0.729	<0.0001
Blood transfusion	1.048	0.768-0.431	0.767
Mother to child	1.699	1.325-2.178	<0.0001
Others	0.652	0.589-0.721	<0.0001

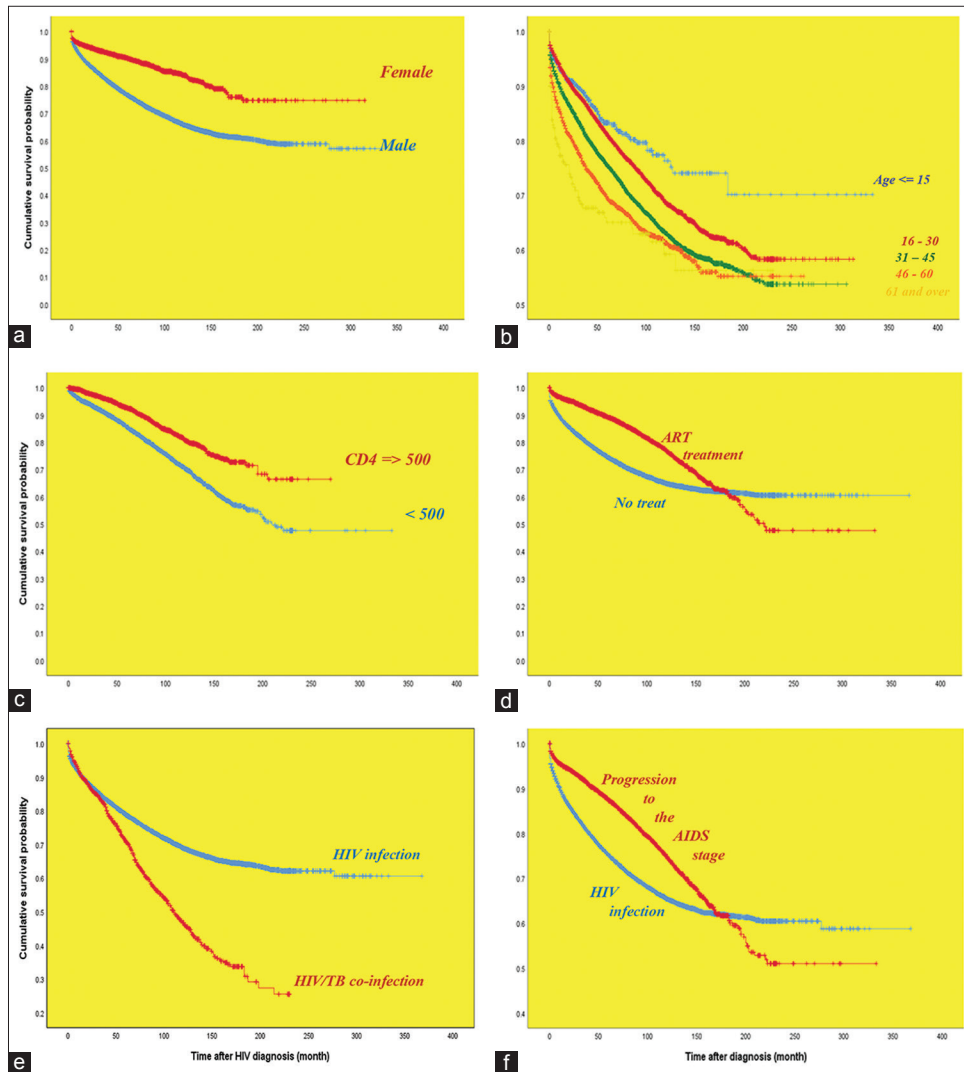
HR=Hazard ratio; AIDS=Acquired immunodeficiency syndrome; TB=Tuberculosis, HIV=Human immunodeficiency virus; CI=Confidence interval; IDU=Injection drug use

rate reduction during this period.<sup>[21-23]</sup> The use of earlier ART initiation and more tolerable regimens can be noted among main cause of increased survival in recent time periods.

The present study demonstrated that ART is associated with lower mortality rate, but being male, age at diagnosis, low CD4 cell count, and TB coinfection were among risk factors associated with higher mortality observed in this study. The risk of death among male patients was higher than that of the female patients, which was similar to other studies. Results of African cohorts show that male gender was independently predictive factor for mortality.<sup>[24]</sup> Other similar studies in China and Tanzania and a meta-analysis of observational studies in low- and middle-income counties reported that the risk of dying from AIDS-related diseases in male patients with HIV/AIDS was higher than that of the female patients.<sup>[24-27]</sup> The reason can be the fact that male patients have more advanced illness, fail to receive timely health-care and interventions, are more likely to drop out of the ART services system, and have poorer clinical outcomes. On the other hand, female patients have better adhere to the treatment delivered by community-based facility.

Our results show that patients who were infected with HIV through sexual route, blood transfusion, or mother to child had lower mortality than those patients infected by IDUs. This finding was similar to other studies that show higher morbidity in infected patients through IDUs than those patients infected by heterosexual transmission<sup>[25,28]</sup> or men who have sex with men.<sup>[29]</sup> This may be because of the presence of coinfection diseases such as hepatitis C and B and poor treatment among these patients, whereas poorer outcome is reported in infected patients with HIV/AIDS through IDU.<sup>[30]</sup>

We find that TB coinfection was also associated with higher risk of mortality (HR: 2.05). Studies conducted in



**Figure 2:** Kaplan–Meier product limits estimates for probability of survival by (a) gender, (b) age at diagnosis, (c) baseline CD4 count, (d) antiretroviral treatment, (e) tuberculosis status, and (f) disease stage status

Somali and Uganda show that relative hazard for death associated with TB were 2.30 and 1.81, respectively.<sup>[31,32]</sup> Manosuthi *et al.* reported that TB coinfection with HIV is a risk factor of death.<sup>[33]</sup> Some other studies have shown the similar relationship between TB coinfection with HIV and risk of death.<sup>[34,35]</sup> This can explain by the fact that the host's immune system in HIV infected patients is suppressed, which can cause to increase the virulence of the mycobacterium and much more severe immunodeficiency status in these patients.

Another risk factor in our study was lower CD4 count, where patients with a CD4 count of <500 cells/mL have a higher risk of mortality compared to those with higher CD4 count. Similar to our finding other studies show that the patients with lower CD4 count have higher risk of mortality compared to patients with lower CD4 count.<sup>[31,36-38]</sup> In contrast, one study shows that CD4 count was not associated with patients' survival; however, the authors concluded that

in their study, the number of patients with high CD4 was limited, and because of low statistical power of the study, they could not have found a significant association.<sup>[39]</sup>

There were limitations to our study. We used observational data from Iran National HIV/AIDS Case Registry System, and it should also be noted that missing data about CD4 cell count, retained in the ART program and other factors, could affect our results, so findings should be interpreted considering the nature of the study design. Furthermore, the survival rate estimated in our study may underestimate the real survival rate in these patients because the estimation was based on time of HIV infection diagnosis where late diagnosis can be occurred in patients who become infected years before they diagnosis time. On the other hand, the large sample size, as a strength of the study, may cause to find significance for any small relationships, and for this reason, interpretation with caution is warranted. Along with all these limitations, in consistent with the literature,

our findings support ongoing improvement of HIV/AIDS control strategies in Iran.

## CONCLUSION

The present study revealed that survival in Iranian HIV/AIDS patients increased in more recent time periods, and ART reduced AIDS-related mortality in these patients. Furthermore, male gender, age at diagnosis, low CD4 cell count, and TB coinfection were the risk factors associated with higher mortality and lower survival in studied population. So, improvements in patients care, increasing ART coverage, earlier ART initiation, more attention to male patients and who infected with HIV through IDU, and more attention to patients with TB coinfection are among strategies that can be effective in increasing patients' survival. Further studies should explore the role of other effective factors in the survival of Iranian patient with HIV/AIDS.

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Nil.

## Conflicts of interest

Dr. Ali-Akbar Haghdoost is the head Deputy of Strategic Planning and Coordination at Iran Ministry of Health and Medical Education, Dr. Mohammad-Mehdi Gooya is the Director General and Head of Center for Communicable Disease Control of the Ministry of Health, and Dr. Parvin Afsar-Kazerooni is the head of the National HIV/AIDS Control Committee.

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