The factors associated with natural disease progression from HIV to AIDS in the absence of ART, a propensity score matching analysis

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Abstract

This study aimed at comparing the factors associated with the natural progression between typical progressors (TPs) and rapid progressors (RPs) in HIV-infected individuals. A retrospective study was conducted on 2095 eligible HIV-infected individuals from 1995 to 2016 in a high-risk area of Henan Province, China. Propensity score matching was used to balance covariates, and the conditional logistic regression analyses were performed to explore the factors of natural disease progression among HIV infectors. A total of 379 pairs of RPs and TPs were matched. The standardised difference values of all covariates were less than 10%. HIV-infected individuals transmitted through sexual transmission (odds ratio (OR) 0.56, 95% confidence interval (CI) 0.36–0.85) were more likely to progress to AIDS compared with those infected through contaminated blood. Older age at diagnosis of HIV-infected individuals (OR 0.72, 95% CI 0.58–0.89) exhibited a faster progression to AIDS. HIV-infected individuals identified through a unique survey (OR 7.01, 95% CI 2.99–16.44) were less likely to progress to AIDS compared with those identified through medical institutions. HIV-infected individuals who had higher baseline CD4+T cell counts (OR 3.37, 95% CI 2.59–4.38) had a slower progression to AIDS. These findings provide evidence for natural disease progression from HIV to AIDS between TPs and RPs.

Introduction

Acquired immune deficiency syndrome (AIDS) is a chronic, potentially fatal spectrum of diseases caused by the human immunodeficiency virus (HIV) and continues to be a serious public health challenge worldwide. Since the beginning of the epidemic, 32.0 million people have died of AIDS-related illnesses and an estimated 37.9 million people globally are living with HIV at the end of 2018 [1]. According to the Chinese Center for Disease Control and Prevention (CDC), 262 442 people have died from AIDS-related illnesses from 1985 to the end of October 2018. There were approximately 849 602 people living with HIV/AIDS at the end of October 2018 in China. The prevention and control of HIV/AIDS still face a daunting challenge.

Nearly all the HIV-infected individuals exhibit a progressive depletion of CD4+T lymphocytes and imbalance in CD4+T-cell homoeostasis, the hall mark of HIV infection. HIV infections appear immunodeficiency, a manifestation of clinical symptoms, and inevitable progression to AIDS eventually. Accumulating evidence indicated that the increase of HIV plasma viral load, decrease of CD4+ lymphocyte counts and concomitant comorbidities were associated with disparities in survival whether receiving antiretroviral therapy (ART) or not [2–4]. With the widespread use of ART, new HIV infections have declined by an estimated 16% and AIDS-related mortality has declined by 33% since 2010 [1]. However, the number of deaths due to HIV/AIDS was still high worldwide in 2018 [1]. These findings emphasise the need to investigate major determinants of HIV/AIDS survival, even though the natural disease progression of HIV infection remains elusive. Hence, it becomes extremely essential and challenging to address and explore the significant factors associated with natural course and progression to immunodeficiency among HIV infections who have not received ART.

According to the duration from HIV to AIDS, disease progression is categorised into rapid, typical and long-term non-progression in the absence of ART [5, 6]. Typical progressors (TPs) have a typical depletion of CD4+T cells and high HIV-RNA, and progression to AIDS occurs within 5–10 years of acquiring HIV. And rapid progressors (RPs) have CD4+T cell counts below 200 cells/mm^3 or develop AIDS-related illnesses within 3–5 years after HIV infection [7, 8]. However, the long-term non-progressors (LTNPs), a very small percentage of HIV-infected individuals (1–5%) remain asymptomatic, with a durable maintenance of CD4+T cell counts ⩾500 cells/mm^3, low levels of viral replication and can remain healthy without significant

progression for more than 10 years without ART [9]. Most of the previous studies primarily focused on the differences of disease progression between LTNPs and TPs/RPs [5, 8]. However, the factors associated with TPs and RPs remain uninvestigated [10, 11]. There might be some differences of natural disease progression between TPs and RPs among some factors.

Propensity score matching (PSM) was proposed by Rosenbaum and Rubin [12] in 1983, as a tool to estimate and reduce the causal effects of measured confounding factors in observational studies. PSM has been widely applied in medical research, especially when a randomised controlled clinical trial is difficult to perform. In this study, we aimed at investigating the differences between TPs and RPs among HIV-infected individuals to identify the factors associated with the natural progression of HIV infection after adjusting for potential confounders by using PSM.

Methods

Study subjects

There were 13 142 HIV/AIDS patients in a high-risk area of Henan Province between 1995 and 2016. A retrospective study was conducted to assess the natural disease progression from HIV to AIDS among HIV-infected individuals in the absence of ART. HIV-positive status of all subjects was confirmed by testing positive for HIV using enzyme-linked immunosorbent assay and western blot analysis. HIV-infected individuals and AIDS patients were followed-up every 6 and 3 months, respectively. Seropositive individuals who had not received ART were selected. Those subjects aged less than 15 years at diagnosis were excluded from the study, as diagnostic criteria and clinical stage are inconsistent among patients less than 15 years and over 15 years.

Measurements and definition

The socio-demographic information including age at diagnosis, gender, census register, marital status, nationality, occupation, education level, disease status (HIV or AIDS), contact with HIV/AIDS patients, spouse HIV status, mode of transmission, sample sources and baseline CD4$^+$T cell counts was recorded. The criteria of AIDS-defining in the study include CD4$^+$T count <200 cells/mm^3 after HIV infection or having at least one symptom after HIV infection such as continuous irregular fever of unknown origin over 38 °C for more than 1 month, pneumocystis pneumonia, oral candidiasis, toxoplasma encephalopathy and so on [5, 6].

All subjects were antiretroviral treatment-naïve, and AIDS-free at the time of diagnosis. HIV-infected individuals with regular follow-up were divided into two groups. TPs were HIV-infected individuals who exhibited one or more of AIDS-defining events within 5–10 years of seroconversion [5]. HIV-infected individuals whose CD4$^+$T cell counts <200 cells/mm^3 or exhibited AIDS-related illness within 5 years of seroconversion were defined as RPs [7].

Propensity score matching

The matching factors included nationality, gender, contact with HIV/AIDS patients and census register. A logistic regression model was used to estimate the propensity score. Subjects were matched within a specified caliper 0.01 based on 1:1 nearest neighbour matching ratio, which means 20% of the standard deviation of propensity score [13]. Moreover, the absolute standardised difference was selected to examine the balance of all measured covariates, because it is more appropriate to assess balance in observational studies compared with the significance test [13–15]. After matching, all the absolute standardised differences were below 10% for all covariates indicated that these covariates exhibit no imbalances among RPs and TPs.

Statistical analysis

Continuous variables were presented as mean (±S.D.), and categorical variables were presented as number (%). For descriptive analysis, a comparison of covariates and explanatory variables between the two groups (RPs vs. TPs) was performed using the χ^2 test or Wilcoxon rank sum test before matching. The post-match comparison was performed using the McNemar test or paired Wilcoxon-signed rank sum test. For the propensity score-matched samples, conditional logistic regression analyses were fitted to estimate the association between potential factors and the natural disease progression of HIV infection. The report of absolute standardised differences was generated using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). All statistical analyses were conducted using SPSS 22.0 software (IBM, Crop, Armonk, NY, USA). A P-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 2095 HIV-infected individuals (TPs: $n = 379$, RPs: $n = 1716$) meeting the eligibility criteria were included. The mean age of TPs was 38.1 (±10.1) years; the mean age of RPs was 40.5 (±9.8) years. All 379 TP HIV-infected individuals were successfully matched. Before matching, the results of covariates comparison between the two groups are shown in Table 1. After matching, absolute standardised differences for all measured covariates were below 10% indicating that these measured covariates were well balanced between TPs and RPs (Fig. 1).

Noticeably, statistically significant differences in descriptive variables including the mode of transmission of HIV, sample sources, age at diagnosis and CD4$^+$T cell counts at baseline before and after matching was observed. Education level also differed significantly between the two groups after matching. No statistically significant differences were observed in potential predictors including occupation, marital status and spouse HIV status after matching (Table 2).

Factors associated with the natural disease progression of HIV infection

Table 3 presents the results of the univariate and multivariate conditional logistic regression analyses of potential factors associated with the natural disease progression of HIV infection. Univariate analyses demonstrated that education level, mode of transmission, sample sources, age at diagnosis and baseline CD4$^+$T cell counts were significantly associated with HIV disease progression ($P < 0.05$). Covariates including occupation, marital status and spouse HIV status were not significantly associated with HIV disease progression ($P > 0.05$).

In the multivariate analyses, education level was no longer statistically significantly associated with HIV disease progression

Table 1. The covariates comparison between RPs and TPs before PSM

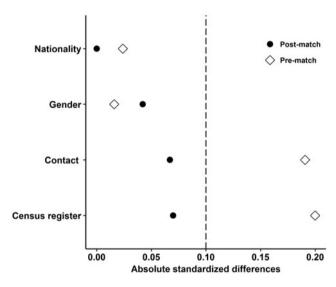| Covariates	RPs n (%)	TPs n (%)	χ^2	P value
Gender			0.071	0.790
Male	923 (53.8)	201 (53.0)		
Female	793 (46.2)	178 (47.0)		
Contact with patients			14.019	<0.001
No	1630 (95.0)	341 (90.0)		
Yes	86 (5.0)	38 (10.0)		
Nationality			0.219	0.639
Han	1706 (99.4)	376 (99.2)		
Others	10 (0.6)	3 (0.8)		
Census register			15.192	<0.001
Permanent residents	1620 (94.4)	337 (88.9)		
Non-permanent residents	96 (5.6)	42 (11.1)		

Fig. 1. Absolute standardised differences for all measured covariates.

($P > 0.05$). HIV-infectors through sexual transmission were more likely to develop AIDS compared with those infected through contaminated blood transmission (odds ratio (OR) 0.56, 95% confidence interval (CI) 0.36–0.85). The HIV-infected individuals who were older at diagnosis were more likely to develop AIDS (OR 0.72, 95% CI 0.58–0.89) as compared with the younger. The HIV-infected individuals identified through unique survey were less likely to develop AIDS compared with subjects diagnosed at a medical institution (OR 7.01, 95% CI 2.99–16.44). HIV-infected individuals who had higher baseline $CD4^+T$ cell counts were less likely to develop AIDS (OR 3.37, 95% CI 2.59–4.38) compared with those who had low $CD4^+T$ cells.

Discussion

In the current study, a conditional logistic regression model was applied to investigate the association between the potential factors and natural disease progression of HIV infection based on the propensity score-matched samples. The analyses revealed that the progression to AIDS was faster in HIV-infected individuals infected through sexual transmission and older ages at diagnosis. Interestingly, HIV-infected individuals who were identified through unique survey were less likely to progress to AIDS after HIV diagnosis. Besides, higher $CD4^+T$ cell counts at baseline delayed the progression to AIDS.

Nevertheless, the results of previous studies investigating the impact of mode of transmission on the progression of HIV infection were inconsistent [16]. Yang et al. [17] suggested that in comparison with HIV-infected individuals infected through contaminated blood transmission, HIV-infected individuals infected through homosexual transmission had significantly lower mortality risk, while HIV-infected individuals whose transmission was through heterosexual transmission exhibited higher mortality risk. Conversely, Chen et al. [18] and Yan et al. [19] found that compared with those infected by blood transmission, HIV-infected individuals infected by homosexual transmission exhibited a significantly higher hazard ratio for progression to AIDS. In their opinions, the high rate of progressing to AIDS among homosexual patients may be due to less social and familial support, stigma, psychological characteristics and so on. In the current study, HIV-infected individuals through sexual transmission were at higher risk of developing AIDS than those through blood transmission. These findings may be attributed to the following reasons. HIV-infected individuals through sexual route exhibited higher plasma HIV load and lower $CD4^+T$ cell counts compared with those infected by blood transmission, resulting in a faster progression to AIDS among those infected by the sexual route [20]. Furthermore, HIV-infected individuals who were infected through sexual transmission may on the other hand have an increased risk of acquiring human papillomavirus, syphilis, candidiasis, herpes and genital ulcer disease [21, 22].

Consistent with previous studies [23, 24], older-aged subjects had a higher risk of disease progression to AIDS in our analyses. Notably in the elderly HIV-infected individuals, an ageing immune system with diminished immune function, low recovery capability and higher comorbidities have been well documented.

Table 2. Patient's demographic characteristics before and after PSM

	Before matching				After matching			
Variables	RPs ($n = 1716$)	TPs ($n = 379$)	Z/χ^2	P value	RPs ($n = 379$)	TPs ($n = 379$)	Z/χ^2	P value
Occupation			9.001	0.003			0.164	0.686
Farmer	1653 (96.3)	352 (92.9)			349 (92.1)	352 (92.9)		
Others	63 (3.7)	27 (7.1)			30 (7.9)	27 (7.1)		
Marital status			11.958	0.003			6.293	0.098
Married	1205 (70.2)	241 (63.6)			238 (62.8)	241 (63.6)		
Divorced or widowed	408 (23.8)	98 (25.9)			116 (30.6)	98 (25.9)		
Unmarried	103 (6.0)	40 (10.6)			25 (6.6)	40 (10.6)		
Education level			4.970	0.174			12.890	0.045
Illiteracy	161 (9.4)	26 (6.9)			47 (12.4)	26 (6.9)		
Primary school	729 (42.5)	163 (43.0)			159 (42.0)	163 (43.0)		
Junior high school	781 (45.5)	174 (45.9)			148 (39.1)	174 (45.9)		
Senior high school or above	45 (2.6)	16 (4.2)			25 (6.6)	16 (4.2)		
Mode of transmission			51.930	<0.001			14.447	0.002
Blood transmission	1404 (81.8)	251 (66.2)			205 (54.1)	251 (66.2)		
Sexual transmission	294 (17.1)	113 (29.8)			161 (42.5)	113 (29.8)		
Others	18 (1.0)	15 (4.0)			13 (3.4)	15 (4.0)		
Sample sources			104.635	<0.001			49.094	<0.001
Medical institutions	283 (16.5)	110 (29.0)			128 (33.8)	110 (29.0)		
VCT	1169 (68.1)	164 (43.3)			215 (56.7)	164 (43.3)		
Unique survey	230 (13.4)	73 (19.3)			13 (3.4)	73 (19.3)		
Others	34 (2.0)	32 (8.4)			23 (6.1)	32 (8.4)		
Spouse HIV status			35.443	<0.001			4.133	0.247
Positive	585 (34.1)	113 (29.8)			121 (31.9)	113 (29.8)		
Negative	734 (42.8)	123 (32.5)			120 (31.7)	123 (32.5)		
Others[a]	397 (23.1)	143 (37.7)			138 (36.4)	143 (37.7)		
Age at diagnosis (year)			3.915	<0.001			4.170	<0.001
15–24	31 (1.8)	28 (7.4)			14 (3.7)	28 (7.4)		
25–34	512 (29.8)	131 (34.6)			106 (28.0)	131 (34.6)		
35–44	703 (41.0)	133 (35.1)			124 (32.7)	133 (35.1)		
≥45	470 (27.4)	87 (23.0)			135 (35.6)	87 (23.0)		
baseline $CD4^+T$ cell counts (cells/mm^3)			14.216	<0.001			10.877	<0.001
<350	1021 (59.5)	76 (20.1)			260 (68.6)	76 (20.1)		
350–500	412 (24.0)	152 (40.1)			76 (20.1)	152 (40.1)		
≥500	283 (16.5)	151 (9.8)			43 (11.3)	151 (9.8)		

VCT, voluntary counselling and testing.
[a]The 'others' included 'no spouse' and 'unknown'.

Moreover, Phillips *et al.* [25] indicated that older HIV-infected individuals exhibited a significantly higher risk of progressing to AIDS than younger regardless of their comparable $CD4^+T$ cell counts and viral loads, which further supports the findings of the current study. Teklu *et al.* [26] and Shrosbree *et al.* [27] found that HIV-infected individuals with older age at the time of diagnosis exhibited a higher risk of late diagnosis, which maybe a cause for faster disease progression among the elderly.

Therefore, an early diagnosis of HIV infection among the elderly is crucial for optimising prognosis. Taken together, older people living with HIV is markedly associated with a number of challenges including physical, clinical and immunological due to the delayed diagnosis, poor treatment outcomes and more frequent medical comorbidities. More attention should be paid to the older population infected with HIV. Besides, both older HIV-infected individuals and their care providers need to

Table 3. Univariate and multivariate analyses of the factors associated with natural disease progression of HIV infections

Variables	Univariable analyses		Multivariable analyses	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Occupation		0.686		
Farmer	1.00			
Others	0.90 (0.53–1.55)			
Marital status		0.100		
Married	1.00			
Divorced or widowed	0.85 (0.62–1.17)	0.316		
Unmarried	1.56 (0.92–2.65)	0.100		
Education level		0.024		
Illiteracy	1.00			
Primary school	1.82 (1.06–3.10)	0.029		
Junior high school	2.08 (1.23–3.51)	0.006		
Senior high school or above	1.15 (0.53–2.54)	0.720		
Mode of transmission		0.001		0.018
Blood transmission	1.00		1.00	
Sexual transmission	0.54 (0.39–0.75)	<0.001	0.56 (0.36–0.85)	0.007
Others	0.99 (0.45–2.17)	0.988	1.27 (0.45–3.59)	0.652
Sample sources		<0.001		<0.001
Medical institutions	1.00		1.00	
VCT	0.89 (0.63–1.26)	0.521	1.06 (0.68–1.66)	0.783
Unique survey	6.78 (3.37–13.66)	<0.001	7.01 (2.99–16.44)	<0.001
Others	0.14 (0.86–2.96)	0.136	1.32 (0.61–2.89)	0.483
Spouse detection		0.827		
Positive	1.00			
Negative	1.09 (0.77–1.55)	0.618		
Others	1.08 (0.79–1.55)	0.565		
Age at diagnosis (year)	0.72 (0.61–0.85)	<0.001	0.72 (0.58–0.89)	0.002
baseline CD4$^+$T cell count (cells/mm^3)	3.22 (2.54–4.08)	<0.001	3.37 (2.59–4.38)	<0.001

VCT, voluntary counselling and testing; OR, odds ratio.

maximise prevention efforts against comorbidities and remain vigilant for early signs of illness.

The CD4$^+$T cell count is recognised as a marker of the degree of immune deficiency in HIV-infected individuals. Notably, as expected, the results showed that HIV-infected individuals with higher CD4$^+$T cell counts at baseline exhibited a slower disease progression in the current study. HIV primarily affects the immune system and causes a progressive depletion of CD4$^+$T cells, and imbalance in CD4$^+$T-cell homoeostasis, and eventually leads to immunodeficiency, a manifestation of clinical symptoms, comorbidities and inevitable progression to AIDS. Goujard *et al.* [28] found that a lower CD4$^+$T cell counts at baseline as a significant potential predictor of rapid progression to AIDS in untreated HIV-infected individuals. Noticeably, for specific immune responses to infection including intracellular pathogens, CD4$^+$T cell counts have been reported to be the most significant predictor of disease progression and survival of HIV infection [29–31].

Besides, the different thresholds of CD4$^+$T cell counts, as a vital criterion, recommending initiation of ART in HIV-infected individuals have been proposed at different times including when the CD4$^+$ less than 200 cells/mm^3 during earlier days, 350 cells/mm^3 in 2008, and 500 cells/mm^3 in 2013. Nevertheless, the WHO released the second edition of the consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection in 2015, recommending lifelong ART for all HIV/AIDS patients regardless of clinical status or CD4$^+$ cell counts to reduce AIDS-related mortality [32]. Constantly, the Chinese health system follows the test-and-treat policy for ART initiation from 2016.

A pivotal strategy, especially in developing countries, is voluntary counselling and testing (VCT), which has emerged to be effective at reducing the risk of acquisition or transmission of HIV through a process involving individualised counselling, with knowledge of one's HIV status [33]. VCT could improve the detection rate of HIV/AIDS and discover new HIV infections

timely. Recent studies have demonstrated that VCT could motivate people to change risky sexual behaviours related to HIV, and increase odds of using condoms and engaging in protected sex among HIV-infected individuals [34–36]. However, in the current study no significant association between VCT and disease progression of HIV infection was observed, possibly due to the low quality of VCT services including shortage of staff, imbalanced allocation of health resources, lack of routine HIV testing and management [36 37]. Also, we found that HIV-infected individuals identified through a unique survey had a slower progression than those diagnosed at a medical institution. This finding may be attributed to the fact that those diagnosed with HIV infection sought medical care to a hospital for other illnesses or clinical symptoms, for HIV infection. Simultaneously, HIV testing motivated by symptoms would cause a late diagnosis for HIV-infected individuals. Further results of previous studies also showed that those diagnosed at medical institutions were at higher risk of late-stage diagnosis of HIV compared with other sample sources [38]. Moreover, it is possible that the HIV-infected individuals who participated in the unique survey received early access to diagnosis, treatment and support, and HIV care.

As a tool to adjust observed confounders in observational studies, PSM may reduce study bias substantially if all potential confounders are observed and considered. However, there are inevitably some other unobserved confounders in the study. Besides, the component ratio of predictors before and after PSM may change. Just as we have observed, the proportion of mode of transmission, sample sources and age at diagnosis in this study have changed after matching, there may be selective bias.

In conclusion, the findings of the current study provide evidence of remarkable association of significant factors including mode of transmission, age at diagnosis, baseline CD4$^+$T cell counts and sample sources with natural disease progression of HIV to AIDS between TPs and RPs in the absence of ART.

References

1. **UNAIDS**. 2019 Global HIV & AIDS statistics. Available at http://www.unaids.org/en/resources/fact-sheet (Accessed 1 December 2019).
2. **Nosyk B** *et al.* (2013) HIV-1 disease progression during highly active antiretroviral therapy: an application using population-level data in British Columbia: 1996–2011. *Journal of Acquired Immune Deficiency Syndromes* **63**, 653–659.
3. **Modjarrad K** *et al.* (2008) Impact of small reductions in plasma HIV RNA levels on the risk of heterosexual transmission and disease progression. *AIDS (London, England)* **22**, 2179–2185.
4. **Chew KW and Bhattacharya D** (2016) Virologic and immunologic aspects of HIV-hepatitis C virus coinfection. *AIDS (London, England)* **30**, 2395–2404.
5. **Wang Z** *et al.* (2012) Similar neutralizing activity in the HIV-1 infected long term non-progressors (LTNPs) and typical progressors (TPs). *Virologica Sinica* **27**, 165–171.
6. **Salgado M** *et al.* (2011) Long-term non-progressors display a greater number of Th17 cells than HIV-infected typical progressors. *Clinical Immunology* **139**, 110–114.
7. **Jarrin I** *et al.* (2015) Does rapid HIV disease progression prior to combination antiretroviral therapy hinder optimal CD4$^+$ T-cell recovery once HIV-1 suppression is achieved? *AIDS (London, England)* **29**, 2323–2333.
8. **Geng W** *et al.* (2011) Rapid disease progression in HIV-1-infected men who have sex with men is negatively correlated with peripheral plasmacytoid dendritic cell counts at the early stage of primary infection. *Journal of Clinical Immunology* **31**, 882–890.
9. **Teixeira SL** *et al.* (2014) Association of the HLA-B*52 allele with non-progression to AIDS in Brazilian HIV-1-infected individuals. *Genes & Immunity* **15**, 256–262.
10. **Jiao Y** *et al.* (2009) The decrease of regulatory T cells correlates with excessive activation and apoptosis of CD8$^+$ T cells in HIV-1-infected typical progressors, but not in long-term non-progressors. *Immunology* **128**, e366–e375.
11. **Li M** *et al.* (2005) Association of CCR5 human haplogroup E with rapid HIV type 1 disease progression. *AIDS Research and Human Retroviruses* **21**, 111–115.
12. **Rosenbaum PR and Rubin DB** (1983) The central role of the propensity score in observational studies for causal effects. *Biometrika* **70**, 41–55.
13. **Austin PC** (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behavioral Research* **46**, 399–424.
14. **Austin PC** (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine* **28**, 3083–3107.
15. **Ahmed A** *et al.* (2007) A propensity-matched study of the effect of diabetes on the natural history of heart failure: variations by sex and age. *Heart (British Cardiac Society)* **93**, 1584–1590.
16. **Sabin CA and Lundgren JD** (2013) The natural history of HIV infection. *Current Opinion in HIV and AIDS* **8**, 311–317.
17. **Yang W** *et al.* (2015) Survival analysis of AIDS patients of 15 years or above years old after initiation antiretroviral treatment in Henan province during 2005 to 2014. *Chinese Journal of Preventive Medicine* **49**, 1061.
18. **Chen L** *et al.* (2015) Rates and risk factors associated with the progression of HIV to AIDS among HIV patients from Zhejiang, China between 2008 and 2012. *AIDS Research and Therapy* **12**, 32.
19. **Yan H** *et al.* (2014) Emerging disparity in HIV/AIDS disease progression and mortality for men who have sex with men, Jiangsu Province, China. *AIDS and Behavior* **18**(Suppl 1), S5–10.
20. **Vlahov D** *et al.* (1998) Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users: plasma viral load and CD4$^+$ cell count. *The Journal of the American Medical Association* **279**, 35–40.
21. **Mukanyangezi MF** *et al.* (2018) Sexual risk behaviour in a cohort of HIV-negative and HIV-positive Rwandan women. *Epidemiology and Infection* **147**, 1–9.
22. **Liu X** *et al.* (2019) Prevalence and genotypes of anal human papillomavirus infection among HIV-positive vs. HIV-negative men in Taizhou, China. *Epidemiology and Infection* **147**, e117.
23. **Hall HI** *et al.* (2006) Determinants of progression to AIDS or death after HIV diagnosis, United States, 1996 to 2001. *Annals of Epidemiology* **16**, 824–833.
24. **Tancredi MV and Waldman EA** (2014) Predictors of progression to AIDS after HIV infection diagnosis in the pre- and post-HAART eras in a Brazilian AIDS-free cohort. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **108**, 408–414.
25. **Phillips A and Pezzotti P** (2004) Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. *AIDS (London, England)* **18**, 51–58.
26. **Teklu AM** *et al.* (2017) Exploratory analysis of time from HIV diagnosis to ART start, factors and effect on survival: a longitudinal follow up study at seven teaching hospitals in Ethiopia. *Ethiopian Journal of Health Sciences* **27**, 17–28.
27. **Shrosbree J** *et al.* (2013) Late HIV diagnosis is a major risk factor for intensive care unit admission in HIV-positive patients: a single centre observational cohort study. *BMC Infectious Diseases* **13**, 23.

28. **Goujard C *et al.*** (2006) CD4 Cell count and HIV DNA level are independent predictors of disease progression after primary HIV type 1 infection in untreated patients. *Clinical Infectious Diseases* **42**, 709–715.

29. **Muller V *et al.*** (2009) African descent is associated with slower CD4 cell count decline in treatment-naive patients of the Swiss HIV Cohort Study. *AIDS (London, England)* **23**, 1269–1276.

30. **Langford SE *et al.*** (2007) Predictors of disease progression in HIV infection: a review. *AIDS Research and Therapy* **4**, 11.

31. **Zhang G *et al.*** (2016) Outcomes and factors associated with survival of patients with HIV/AIDS initiating antiretroviral treatment in Liangshan Prefecture, southwest of China: a retrospective cohort study from 2005 to 2013. *Medicine (Baltimore)* **95**, e3969.

32. **Bellino S *et al.*** (2019) Trends of hospitalisations rates in a cohort of HIV-infected persons followed in an Italian hospital from 1998 to 2016. *Epidemiology and Infection* **147**, e89.

33. **World Health Organization**. Scaling-up HIV testing and counselling services: a toolkit for programme managers. Available at https://apps.who.int/iris/handle/10665/43245.

34. **Coates TJ *et al.*** (2014) Effect of community-based voluntary counselling and testing on HIV incidence and social and behavioural outcomes (NIMH Project Accept; HPTN 043): a cluster-randomised trial. *The Lancet Global Health* **2**, e267–e277.

35. **Fonner VA *et al.*** (2013) Voluntary counseling and testing (VCT) for changing HIV-related risk behavior in developing countries. *Cochrane Database Systematic Reviews* **30**, 382–384.

36. **Cawley C *et al.*** (2014) The impact of voluntary counselling and testing services on sexual behaviour change and HIV incidence: observations from a cohort study in rural Tanzania. *BMC Infectious Diseases* **14**, 159.

37. **Apanga PA *et al.*** (2015) Factors influencing uptake of voluntary counselling and testing services for HIV/AIDS in the Lower Manya Krobo Municipality (LMKM) in the Eastern Region of Ghana: a cross-sectional household survey. *Journal of Health, Population and Nutrition* **33**, 23.

38. **An Q *et al.*** (2015) Trends and differences among three new indicators of HIV infection progression. *Public Health Reports* **130**, 468–474.