Research Letter

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Antiretroviral therapy initiation within 7 and 8–30 days post-HIV diagnosis demonstrates similar benefits in resource-limited settings

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We estimated the optimum time to initiate antiretroviral therapy (ART) in a retrospective observational cohort. We observed that ART initiation 7 days or less ($n = 817$) and 8–30 days ($n = 1009$) were the most important factors with viral suppression, and had similar viral suppression rate, CD4$^+$ T-cell count increase and fractions of individuals with links at least 4 and individuals linked to recent HIV infection in HIV molecular networks. This study provides real-world evidence on the benefits of rapid ART initiation in resource-limited setting.

The WHO proposed 'rapid ART initiation' in 2017 and recommended that patients with no contraindication to rapid ART initiation should be offered ART initiation within 7 days of HIV diagnosis [1]. However, the timeframe of rapid ART initiation was not especially emphasized in some low-income and middle-income countries (LMIC), especially LMIC with a low HIV burden [2,3]. As rapid ART initiation is resource-intensive [4], and it is not easy or practical to implement this strategy in realistic resource-limited public settings. Therefore, the major concern now focuses on how rapidly to initiate ART to obtain maximum benefits in realistic, resource-limited public settings.

A retrospective observational cohort was conducted among people with HIV (PWH) who received a confirmed diagnosis of HIV infection in Shenyang city, a moderately HIV-prevalent province in China (PWH >10 000) [5], between 1 January 2016 and 31 December 2019. All patients who initiated ART were categorized into three groups according to the time of ART initiation, including the 7 days or less group (rapid ART initiation), the 8–30 days group, and the greater than 30 days group (deferred ART initiation). The baseline demographic, epidemiological data, and plasma samples were collected at the time of diagnosis, and clinical data were also collected until 31 December 2020.

In this study, we assessed the impact of ART initiation time on individual and community benefits in resource-limited settings. Viral suppression (<50 copies/ml [6]) rate within 180 or 360 days post-ART initiation (DPA) and CD4$^+$ T-cell count increase within 180–360 or after 360 DPA were detected to assess individual clinical benefits. On the basis of the baseline HIV *pol* sequence (HXB2: 2253–3300 base pairs), the lower risk of HIV transmission can be assessed as public health benefits by inferring molecular networks using HIV-TRACE [7]. The number of links between individuals in the network has been considered the most direct indicator to assess the risk of HIV transmission [8]. The other indicator is based on the contribution of individuals to recent HIV infection (RHI) in the network, which was determined by HIV-1 Limiting Antigen Avidity tests [9]. For example, a newly diagnosed RHI in 2017 can only be infected by those individuals who were infected with HIV before 2017 (inclusive). Finally, we can compare the proportion of individuals with a high risk of transmitting HIV in each group.

(The individuals with link ≥4 or the individuals that contributed to RHI in each group / All the individuals in each group involved in building the molecular network)

A total of 2842 patients were included in this study; 93.1% were men. The median age was 32 years [interquartile range (IQR) = 26–45]. Further, 81.9% were self-reported to be MSM, and 33.1% cases were RHI. 87.8% initiated ART and the number of individuals in the 7 days or less group, the 8–30 days group, and the greater than 30 days group were 817, 1009; and 668, respectively. 12.2% PWH did not initiate ART or lost follow-up. The median time of ART initiation was 5 days (IQR: 1–6), 16 days (IQR: 12–22), and 61 days (IQR: 40–165). 71.3% PWH who initiated ART applied the standard first-line ART regimen (Tenofovir/zidovudine + Lamivudine + Efavirenz) in China [3] (Supplementary Table 1, http://links.lww.com/QAD/C580).

Cox proportional hazards regression was used to evaluate determinants of viral suppression rate. Two thousand one hundred and two (95%) PWH with viral suppression were recorded, for an overall viral suppression rate of 11.3 per 100 person-months. ART initiation within 7 days of HIV diagnosis was the most important factor (adjusted hazard ratio = 1.268, $P < 0.0001$), and ART initiation within 8–30 days of HIV diagnosis was a modest important factor (adjusted hazard ratio = 1.132, $P = 0.017$) relative to ART initiation after 30 days of HIV diagnosis (Supplementary Table 2, http://links.lww.com/QAD/C581). There was no significant difference in viral suppression rate between the 7 days or less group and the 8–30 days group, regardless of within 180 or 360 DPA, and both

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Table 1. The virological and CD4$^+$ T-cell response and HIV transmission risk of the people with HIV in antiretroviral therapy groups

Characteristics	Total ($n=2494$)	%	7 days or less group ($n=817$)	8–30 days group ($n=1009$)	>30 days group ($n=668$)	7 days vs. greater than 30 days *P* value	8–30 days vs. greater than 30 days *P* value
Viral suppression rate (<50 copies/ml)	2102	84.3	$n=687$	$n=863$	$n=552$		
within 180 DPA	1237	49.6	431 (62.7)	510 (59.1)	296 (53.6)	0.0012	0.0427
within 360 DPA	1721	69.0	581 (84.6)	709 (82.2)	431 (78.1)	0.0035	0.059
CD4$^+$ T-cell count increase (cells/μl)							
Total	1304	52.3	$n=444$	$n=532$	$n=328$		
Within 180–360 DPA			158 ± 156	141 ± 186	105 ± 181	<0.0001	0.004
Total	1259	50.5	$n=393$	$n=517$	$n=349$		
After 360 DPA			224 ± 191	201 ± 196	169 ± 259	0.001	0.04
HIV transmission risk							
Total	2312	92.7	$n=756$	$n=941$	$n=615$		
Link at least 4	146	5.9	37 (4.9)	54 (5.7)	55 (8.9)	0.0033	0.0163
Linking to RHI	385	15.4	110 (14.6)	151 (16.0)	124 (20.2)	0.0062	0.0378

ART, antiretroviral therapy; DPA, days post-ART initiation; PWH, people with HIV; RHI, recent HIV infection.

were significantly higher than that of the more than 30 days group (Table 1).

However, there were still no significant differences on CD4$^+$T-cell count increase between the 7 days or less and 8–30 days groups, regardless of within 180–360 or after 360 DPA, and both were also significantly higher than those in the more than 30 days group (Table 1).

The molecular networks of the three major subtypes [CRF01_AE; CRF07_BC; and B (92.9%)] was inferred [10]. The third quartile of the number of links for all individuals with links greater than 1 in the network was 4; therefore, link at least 4 was identified as the standard for high risk of transmitting HIV. The proportion of individuals with link at least 4 in the 7 days or less group and 8–30 days group were similar and significantly lower than that in the more than 30 days group. The fraction of individuals linked to RHI in the 7 days or less and 8–30 days groups were also similar and significantly lower than those in the more than 30 days group (Table 1).

Previous studies only focused on the benefits of rapid ART initiation [11–14] or ART initiation within 30 days after HIV diagnosis [15,16]. Our study was the first to compare the benefits of ART initiation within 7 and 8–30 days after HIV diagnosis at the individual clinical and public health levels. We found that ART initiation within 30 days of HIV diagnosis could achieve benefits similar to those of ART initiation within 7 days of HIV diagnosis in resource-limited settings. In addition, we also found that the individuals in the more than 30 days were most likely to be less than 30 years old and have better immune status (higher baseline CD4$^+$ T-cell count), which suggested that relatively good physical condition could be obstacle to immediate ART initiation (Supplementary Table 1, http://links.lww.com/QAD/C580). This study is also another good example of applying molecular network technology to evaluate public health benefits of ART initiation time by assessing the risk of HIV transmission [8]. More importantly, our study is a real-world, whole population observation study, rather than a cohort study with specific research purposes, and therefore, likely reflects the real effect of different ART initiation times.

Our study has some limitations. First, inferred linkage in molecular network does not prove transmission. Second, we were unable to determine, which regimens better contributed to positive outcomes because of the different ART regimens of PWH in each ART group. Third, we did not analyze the impact of the time of ART initiation time on the virtual reservoir, the viral setpoint, immune damage and so on.

Overall, ART initiation within 7 days and 8–30 days of HIV diagnosis had similar benefits in terms of ART efficacy and control of HIV transmission, both of which were superior to deferred ART initiation. This study provides important evidence to guide rapid ART initiation in real-world, resource-limited public settings.

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Conflicts of interest

There are no conflicts of interest.

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