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Rapidly Spreading Human Immunodeficiency Virus Epidemic Among Older Males and Associated Factors: A Large-scale Prospective Cohort Study in Rural Southwest China

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Background: Increasing risk of human immunodeficiency virus (HIV) heterosexual transmission can raise the potential for a more diffuse and generalized epidemic. In response to the paucity of data on HIV incidence among heterosexuals in China, we conducted a large-scale, population-based cohort study located in rural southwest China.

Methods: Baseline enrollment for the study was conducted from 2013 to 2014 and follow-up at 12 months was from 2014 to 2015 among adults 20 years or older in 3 rural counties of Southwest China. Study participants were informed of the study by brochures and leaflets distributed in outreach activities. Interviews and blood collection were conducted in private rooms. Blood samples were tested for HIV infection.

Results: The HIV prevalence of the sample was 0.29% (95% confidence interval [CI], 0.27–0.30) (2063 of 722,795) among the total adult population of 1,090,296 potential participants 20 years or older at baseline. Of the 720,732 individuals who tested HIV-negative at baseline, 493,990 (69%) completed the follow-up. Overall HIV incidence was 2.73 (95% CI, 2.38–3.08) per 10,000 person-years (PY) (235 of 860,627 PY). Human immunodeficiency virus incidence was associated with males, older age, less than secondary schooling and not currently being married. Human immunodeficiency virus incidence was 71.28 (95% CI, 35.21–107.35) per 10,000 PY among males aged 50 to 69 years who had less than secondary schooling and were divorced or widowed. Heterosexual sex was the dominant transmission mode for HIV seroconversions (99.0%).

Conclusions: Older heterosexual males were at disproportionate risk of HIV infection. Health authorities in China need to develop and implement innovative interventions suitable for the broader population of older heterosexuals.

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Drug abuse reemerged as a problem in China when an open-door policy was adopted in the late 1980s.[1–5] The first human immunodeficiency virus (HIV) outbreak among people who inject drugs (PWID) in China was discovered in Yunnan in 1989.[6] Thereafter, HIV transmission spread rapidly among PWID residing along the major drug-trafficking routes to other provinces in Southern and Western China.[7–12] Since China adopted elements of a free market economy in 1978, commercial sex activities have increased dramatically across the country.[13] The proportion of newly reported HIV/acquired immune deficiency syndrome (AIDS) infections through heterosexual sex increased from 39% in 2007 to 66% in 2014, whereas new HIV/AIDS infections attributed to injection drug use decreased from 29% in 2007 to 6% in 2014.[14,15] Generally, the HIV epidemic in China has been similar to other Asian countries, starting as a drug-driven epidemic and shifting to one driven predominantly by sexually transmission.[16–22] Human immunodeficiency virus incidence attributed to male-male and male-female sex has increased rapidly in China.[14–16]

Guangxi is the homeland of the Zhuang nationality, has approximately 50 million people, and is a developing area in China. Guangxi is located in Southwest China bordering Vietnam and is

in close proximity to the "Golden Triangle," an area between Myanmar, Laos, and Thailand known for the manufacturing of illicit drugs.[7–10] Guangxi lies along the eastern drug-trafficking route linking Yunnan (adjacent to the Golden Triangle), Guangdong, and Hong Kong. Guangxi's initial HIV epidemic was fueled by PWID, who accounted for the majority of reported HIV/AIDS cases in the late 1990s (Supplementary Figure 1a, http://links.lww.com/OLQ/A325).[15] In the meantime, the HIV epidemic has shifted to predominantly heterosexual transmission, accounting for less than 10% of new cases in 2000 to over 90% of new cases in 2013 (Supplementary Figure 1a, http://links.lww.com/OLQ/A325).[15] The demographics of individuals most afflicted by the epidemic have also shifted. In the same time frame, the elder population (≥50 years of age) as a proportion of new HIV cases increased from less than 4% in 2000 to over 40% in 2013 (Supplementary Figure 1b, http://links.lww.com/OLQ/A326).[15] In 2013, 10,877 cases of HIV/AIDS were reported in Guangxi.[15]

It is important to study the rapid evolution of the HIV epidemic in Guangxi to understand the specific characteristics and factors contributing to these dramatic changes. These research findings will help to explain the epidemic shift and guide targeted interventions for the most vulnerable populations. During the earlier phases of the epidemic, high-risk populations were largely restricted to paid blood donors and PWID. In the current sexually driven epidemic, risk groups are much broader. Population-based incidence rates of HIV infection are still difficult to obtain in both China and elsewhere in the world. In response to this gap in the literature, the aim of this study was to use a large-scale population-based prospective cohort study to evaluate HIV incidence and demographic correlates in 3 rural counties in the Guangxi Zhuang Autonomous Region, a provincial-level region located in southwest China that reports 12% of all new cases of HIV in China.[15]

METHODS

Study Design and Study Population

Under the support of the National Mega Project on Infectious Disease Prevention and Control, we designed a population-based cohort study in 3 rural counties in Guangxi. The baseline survey was conducted from January 2013 to March 2014 and then the follow-up at 12 months among individuals who tested HIV-negative at baseline was conducted from October 2014 to June 2015. Participants were informed of this study by brochures and leaflets distributed in outreach activities. Local health staff were trained to distribute recruitment information to potential participants. Recruitment materials included basic knowledge of HIV, transmission and prevention, counseling and testing, care and national free treatment services. All participants, regardless of HIV diagnosis, were contacted directly by outreach workers and indirectly through word of mouth to invite them to join the study for testing HIV. There was no incentive for study participation. Eligibility criteria included residency in 1 of the 3 counties, 20 years or older, willing to participate, and provision of informed consent. All participants who met the study criteria then received HIV pretest counseling, had blood drawn to test for HIV antibody, and were given HIV testing results and post-testing counseling. Interviews and blood collection were conducted in private rooms at township hospitals and village clinics. All individuals who tested positive for HIV during the study were introduced to the National AIDS Control and Care policy by health staff and then referred to the National Free Antiretroviral Treatment Program. To maintain high follow-up retention rates, outreach workers made telephone calls and/or home visits if a participant missed initial follow-up testing. The study protocol and informed consent form were approved by the institutional review board of the Guangxi Center for Disease Control and Prevention.

Of 1,090,296 potential participants 20 years or older, 722,795 study participants completed the baseline survey. Two thousand sixty-three participants tested positive for HIV during the baseline survey. Of the 720,732 participants who tested HIV-negative at baseline, 493,990 completed the follow-up. Two hundred thirty-five seroconversions were observed during the follow-up. Reasons for participant nonenrollment and lost to follow-up were not documented.

Data Collection

Questionnaire-based interviews were conducted in a private room. Trained health staff conducted the interviews. Each study participant was assigned a unique and confidential identification number for the questionnaire and blood samples. Questionnaire data included age, ethnicity, education, marital status, and occupation. If participant HIV test results were positive, additional questions about transmission route were asked, such as heterosexual sex, male-to-male sex, and drug injection. Questions concerning HIV transmission modes were asked to guide the development of future interventions.

Laboratory Testing

Blood samples were tested for HIV infection. Human immunodeficiency virus antibody was screened in each blood sample by enzyme-linked immunosorbent assay (Diagnostic Kit for Antibody to Human Immunodeficiency Virus, Beijing WANTAI Biological Pharmacy Enterprise Co. Ltd, China; and Genscreen ULTRA HIV Ag-Ab, Bio-Rad Laboratories, USA), and was confirmed by HIV Western Blot confirmation (MP Diagnostics HIV BLOT2.2, MP Biomedicals Asia Pacific Pte. Ltd).

Statistical Analysis

Questionnaire-based data and biological testing results were recorded, double-entered and compared with SPSS version 17.0 (SPSS, Inc., Chicago, IL). Human immunodeficiency virus prevalence at baseline was calculated as the number of HIV infections/number of participants enrolled. The incidence of HIV was estimated by using the number of seroconversions detected within the follow-up period as the numerator and the cohort's total number of person-years (PY) exposure to the risk of transmission as the dominator. To identify factors associated with HIV infection and incidence, logistic regression and Cox regression models were used, respectively. Adjusted regression models included the following control variable covariates: age, sex, ethnicity, education, marital status, occupation, and county. Statistical significance was defined as a P less than 0.05 (2-tailed).

Ethics Statement

The study was approved by the institutional review board of the Guangxi Center for Disease Control and Prevention.

RESULTS

General Characteristics of Study Population

Of 1,090,296 potential participants 20 years or older, 66.3% (722,795 of 1,090,296) participated in the population-based cohort study. Of 722,795 study participants who completed the baseline survey, participants older than 50 years represented 36.0%. The percentage of males was 48.9%. Participants (62.1% and 36.3%) were ethnically Han and Zhuang, respectively. The

percentage of participants with no schooling, primary schooling and secondary schooling or above was 5.7%, 33.5% and 60.8%, respectively. Participants, 86.4%, 9.9% and 3.7%, were currently married, single, and divorced/widowed, respectively. The occupation for most participants (89.2%) was agricultural farming.

HIV Infection Rates at Baseline

The HIV infection prevalence was 0.29% (95% confidence interval [CI], 0.27–0.30) (2063 of 722,795) among all study participants (group aged ≥20 years) at baseline. Table 1 presents the factors (age, sex, ethnicity, education, marital status, occupation, and county) associated with HIV infection at baseline. Factors significantly associated with HIV infection in the final multivariable logistic model was aged 50 to 59 years (adjusted odds ratio [AOR], 1.32; 95% CI, 1.15–1.52), aged 60 to 69 years (AOR, 1.44; 95% CI, 1.24–1.68), male (AOR, 2.68; 95% CI, 2.43–2.96), primary school education attainment (AOR, 1.43; 95% CI, 1.29–1.58), never married (AOR, 3.59; 95% CI, 3.09–4.18), divorced/widowed (AOR, 6.23; 95% CI, 5.46–7.11), county B (AOR, 0.2; 95% CI, 0.18–0.23), and county C (AOR, 0.21; 95% CI, 0.19–0.24). Supplemental Table 1, http://links.lww.com/OLQ/A327 presents HIV prevalence by sex and age groups.

HIV Incidence

Of the 720,732 study participants who tested HIV-negative at baseline, 493,990 (69%) completed the follow-up. The median duration of follow-up was 1.7 years (Q1–Q3, 1.4–1.8 years) among those who returned for follow-up. Baseline demographics between individuals followed up and lost to follow-up were generally comparable, though individuals lost to follow-up were slightly younger, had higher educational attainment, and were less likely to be from county "A" (Table 2).

Table 3 presents the factors associated with HIV incidence in the follow-up study. Overall HIV incidence was 2.73 (95% CI, 2.38–3.08) per 10,000 PY (235 of 860,627 PY). The bivariate analysis using the Cox regression model indicated that HIV incidence was associated with age, sex, education, and marital status. After adjustments in the final Cox regression model, age 40 to 49 years (Adjusted hazard ratio, 1.74; 95% CI, 1.04–2.92), age 50 to 59 years (AHR, 1.96; 95% CI, 1.15–3.33), age 60 to 69 years (AHR, 3.47; 95% CI, 2.07–5.82), male (AHR, 4.41; 95% CI, 3.22–6.05), no schooling (AHR, 2.36; 95% CI, 1.34–4.13), primary school (AHR, 2.35; 95% CI, 1.69–3.28), single (AHR, 5.98; 95% CI, 3.81–9.40), and divorced/widowed (AHR, 5.19; 95% CI, 3.56–7.57) were significantly associated with HIV incidence. Human immunodeficiency virus incidence was 7.47 (95% CI, 5.97–8.98), 8.51 (95% CI, 7.04–9.98), and 35.61 (95% CI, 22.65–48.58) per 10,000 PY among males aged 50 to 69 years, males with less than secondary schooling, and males divorced or widowed, respectively. Human immunodeficiency virus incidence was 71.28 (95% CI, 35.21–107.35) per 10,000 years among males aged 50 to 69 years who had less than secondary schooling and were divorced or widowed. Supplemental Table 2, http://links.lww.com/OLQ/A328 presents HIV incidence by sex and age group.

Of 235 individuals who had HIV seroconversions during the follow-up period, heterosexual sex was the identified mode of transmission for 99.0% of cases, followed by male-to-male sex (1.0%). Among males who seroconverted, 79% had sex with female sex workers and 18% had sex with casual sexual partners,

TABLE 1. HIV Infection Among Study Participants at Baseline (Adults Aged ≥20 Years) in Guangxi China

Factors	No. Participants, n (%)		HIV Prevalence (n)	OR (95% CI)	*P*	AOR* (95% CI)	*P*
Total	72,2795	100.0%	0.29% (2063)				
Age, y							
30–39	143,347	19.8%	0.28% (397)				
20–29	155,234	21.5%	0.06% (94)	0.22 (0.17–0.27)	<0.001	0.16 (0.12–0.20)	<0.001
40–49	163,793	22.7%	0.29% (482)	1.06 (0.93–1.21)	0.370	1.08 (0.94–1.24)	0.253
50–59	113,485	15.7%	0.40% (453)	1.44 (1.26–1.65)	<0.001	1.32 (1.15–1.52)	<0.001
60–69	83,950	11.6%	0.53% (443)	1.91 (1.67–2.19)	<0.001	1.44 (1.24–1.68)	<0.001
≥70	62,986	8.7%	0.31% (194)	1.11 (0.94–1.32)	0.224	0.61 (0.50–0.74)	<0.001
Sex							
Female	369,584	51.1%	0.17% (612)				
Male	353,211	48.9%	0.41% (1451)	2.49 (2.26–2.73)	<0.001	2.68 (2.43–2.96)	<0.001
Ethnicity		0.0%					
Zhuang	262,694	36.3%	0.33% (872)				
Han	449,167	62.1%	0.26% (1157)	0.78 (0.71–0.85)	<0.001	1.09 (0.99–1.20)	0.068
Other	10,934	1.5%	0.31% (34)	0.94 (0.66–1.32)	0.708	0.85 (0.60–1.21)	0.367
Education							
Secondary school or above	439,462	60.8%	0.21% (922)				
No schooling	40,851	5.7%	0.32% (129)	1.51 (1.25–1.81)	<0.001	1.16 (0.94–1.43)	0.160
Primary school	242,482	33.5%	0.42% (1012)	1.99 (1.82–2.18)	<0.001	1.43 (1.29–1.58)	<0.001
Marital status							
Current married	624,444	86.4%	0.24% (1472)				
Single	71,868	9.9%	0.35% (252)	1.49 (1.30–1.70)	<0.001	3.59 (3.09–4.18)	<0.001
Divorced/widowed	26,483	3.7%	1.28% (339)	5.49 (4.87–6.18)	<0.001	6.23 (5.46–7.11)	<0.001
Farmer							
No	78,079	10.8%	0.36% (284)				
Yes	644,716	89.2%	0.28% (1779)	0.76 (0.67–0.86)	<0.001	1.00 (0.87–1.14)	0.980
County							
A	153,280	21.2%	0.79% (1206)				
B	341,703	47.3%	0.15% (514)	0.19 (0.17–0.21)	<0.001	0.20 (0.18–0.23)	<0.001
C	227,812	31.5%	0.15% (343)	0.19 (0.17–0.21)	<0.001	0.21 (0.19–0.24)	<0.001

*Covariates of the adjusted model included: age, sex, ethnicity, education, marital status, farmer and county.

TABLE 2. Baseline Demographics Between Individuals Followed Up and Lost to Follow-up Among Participants Who Tested HIV-Negative at Baseline (Adults Aged ≥20 Years) in Guangxi, China

Factor	Total	Lost to Follow-up		Followed up		χ^2	*P*
Total	720,732	226742	%	493990	%		
Age, y						22647.2	<0.001
30–39	142951	51143	23	91808	19		
20–29	155139	68406	30	86733	18		
40–49	163311	46850	21	116461	24		
50–59	113032	25557	11	87475	18		
60–69	83507	16764	7	66743	14		
≥70	62792	18022	8	44770	9		
Sex						588.3	<0.001
Female	368972	111299	49	257673	52		
Male	351760	115443	51	236317	48		
Ethnicity						1854.9	<0.001
Zhuang	261822	78816	35	183006	37		
Han	448010	142555	63	305455	62		
Other	10900	5371	2	5529	1		
Education						10381.6	<0.001
Secondary school or above	438540	156007	69	282533	57		
No schooling	40722	13663	6	27059	5		
Primary school	241470	57072	25	184398	37		
Marital status						11518.3	<0.001
Current married	622972	184699	81	438273	89		
Single	71616	35122	15	36494	7		
Divorced/widowed	26144	6921	3	19223	4		
Farmer						3468.8	<0.001
No	77795	31679	14	46116	9		
Yes	642937	195063	86	447874	91		
County						22275.9	<0.001
A	152074	24085	11	127989	26		
B	341189	117911	52	223278	45		
C	227469	84746	37	142723	29		

but not sex workers. Among females who seroconverted, 62% and 37% were infected through their spouse or steady sexual partners, and casual sexual partners, respectively.

DISCUSSION

Our study indicated that the HIV prevalence was 0.29% and HIV incidence was 2.73 per 10,000 PY among adults of the general population in a population-based, large-scale prospective cohort study. The major mode of HIV transmission was heterosexual sex. Findings from this population-based study suggest that HIV is spreading rapidly among older heterosexual adults in rural southwest China. From an international perspective, the HIV incidence rate among individuals aged 50 to 69 years in this study was 10 times greater than that of their counterparts in the United States.[17] One alarming finding in our study was that the HIV incidence rates among males aged 50 to 69 years, males with less than secondary schooling, and males divorced or widowed was comparable with that of serious HIV epidemics in Africa, such as in Rwanda, which has a national HIV incidence rate of 27 per 10,000 PY.[18] In fact, HIV incidence among males aged 50 to 69 years with less than secondary schooling and who were divorced or widowed was much higher than that of Rwanda's national HIV incidence.[18] Since heterosexual sex is the main mode of transmission bridging the HIV epidemic from high-risk populations to the general population, the HIV epidemic in China appears to have entered a new phase. Male-to-male sexual transmission has been rapidly increasing in cities and developed areas in China over the past decade, but results from this large-scale observational cohort study indicate that the virus is already spreading beyond traditional high-risk populations, to groups like older heterosexual males in developing parts of southwest China.

Prior to 2007, HIV/AIDS transmission in Southwest China was primarily attributed to unsafe injection practices. Due to greater injection drug use activities, county A had significantly higher HIV prevalence than the other counties. However, after the implementation of comprehensive harm reduction programs, the majority of reported HIV infections in Southwest China since 2007 have been attributed to sexual transmission.[14] Our study results show that HIV incidence was comparable among the 3 counties, thus supporting the observation that the HIV epidemic which began as a drug-driven epidemic has shifted to one driven predominantly by sexual contact. These new changes pose greater challenges than ever before in China's AIDS control efforts.

Our cohort study also found that HIV infection was much higher among older heterosexual males, especially among those with low education and who were not currently married. These results underscore the fact that many older people over 50 years of age are still sexually active. Older adults, especially older men without a spouse or steady sex partner may seek sex with female commercial sex workers or casual partners.[19–21] The reason for older men engaging in unprotected sex may be related to poor education about safer sex practices and underestimating their risk of contracting HIV.[22,23] Another reason may be that older men might be more likely to use male erectile dysfunction medications that improve sexual function. By prolonging intercourse, erectile dysfunction medications may allow more bodily fluids to transfer, and thus increase the possibility of HIV sexual transmission.[19,20,24] These drugs labeled as aphrodisiacs may be produced illegally by underground workshops and sold without regulation.[19,20] Older males with lower levels of education and inconsistent

TABLE 3. HIV Incidence of Study Participants in a Follow-Up Study (Adults Aged ≥20 Years) in Guangxi China

Factor	No. Seroconversions	PYs	Incidence Rate (/10,000 PYs)	HR (95% CI)	*P*	AHR* (95% CI)	*P*
Total	235	860,627.0	2.73				
Age, y							
30–39	22	159,501.5	1.38				
20–29	5	151,613.0	0.33	0.24 (0.09–0.64)	0.004	0.12 (0.05–0.34)	<0.001
40–49	48	202,827.2	2.37	1.71 (1.03–2.84)	0.037	1.74 (1.04–2.92)	0.034
50–59	46	152,058.4	3.03	2.18 (1.31–3.63)	0.003	1.96 (1.15–3.33)	0.014
60–69	81	117,616.3	6.89	5.03 (3.14–8.05)	<0.001	3.47 (2.07–5.82)	<0.001
≥70	33	77,010.5	4.29	3.08 (1.79–5.28)	<0.001	1.45 (0.79–2.68)	0.232
Sex							
Female	55	447,076.9	1.23				
Male	180	413,550.1	4.35	3.56 (2.63–4.81)	<0.001	4.41 (3.22–6.05)	<0.001
Ethnicity							
Zhuang	89	322,375.6	2.76				
Han	145	528,864.5	2.74	0.99 (0.76–1.29)	0.934	1.23 (0.93–1.64)	0.143
Other	1	9386.9	1.07	0.37 (0.05–2.68)	0.328	0.52 (0.07–3.76)	0.519
Education							
Secondary school or above	62	492,534.0	1.26				
No schooling	22	47,145.5	4.67	3.69 (2.27–6)	<0.001	2.36 (1.34–4.13)	0.003
Primary school	151	320,947.5	4.7	3.71 (2.76–4.98)	<0.001	2.35 (1.69–3.28)	<0.001
Marital status							
Current married	168	762,620.4	2.2				
Single	27	64,746.0	4.17	1.92 (1.28–2.88)	0.002	5.98 (3.81–9.40)	<0.001
Divorced/widowed	40	33,260.6	12.03	5.42 (3.84–7.66)	<0.001	5.19 (3.56–7.57)	<0.001
Farmer							
No	16	80,652.1	1.98				
Yes	219	779,974.9	2.81	1.42 (0.86–2.36)	0.175	1.24 (0.73–2.1)	0.432
County							
A	67	213,674.6	3.14				
B	83	384,131.2	2.16	0.73 (0.53–1.01)	0.057	0.72 (0.52–1.02)	0.062
C	85	262,821.2	3.23	1.14 (0.83–1.57)	0.433	1.36 (0.98–1.88)	0.065

*Covariates of the adjusted model included: age, sex, ethnicity, education, marital status, farmer and county.

condom use with females reported that aphrodisiacs helped sexual performance. Our previous study found scientific evidence that aphrodisiac usage was associated with higher HIV prevalence among older males, especially older male clients of low-priced female sex workers.[19,20] Unfortunately, health promotion staff are often face difficulties implementing HIV interventions with female sex workers because most low-priced female sex workers have no fixed locations for sex work.[19–21] Meanwhile, our study found that most females were infected through their spouse or steady sexual partners. National and regional observational cohort studies in China have shown reductions in the risk of HIV transmission in serodiscordant couples if the index patient received antiretroviral therapy,[25,26] and such programs have been implemented for the prevention of HIV transmission within serodiscordant couples in China. Current HIV education and prevention efforts in China are primarily focused on traditional high-risk populations such as PWID, men who have sex with MSM, and female sex workers, all of whom are predominantly young persons. Thus, these findings point to a serious need for new prevention efforts focused on older individuals of the general population.

Our study has several limitations. First, the duration of the follow-up was limited and longer-term trends of HIV incidence require further study. Second, we did not collect information about risk behaviors which may have confounded measures of association in the study. For example, it is unknown if follow-up rates differed by HIV risk. Third, asking questions regarding risk only of those who tested positive for HIV limited our ability to fully describe the baseline sample. Fourth, this cohort study was conducted in 3 rural counties in Guangxi, Southwest China, which only represents 12% of all new cases of HIV in China. In addition, our study methods might have influenced the generalizability of the results. For example, self-selection, a 69% follow-up rate, and differential follow-up rates between the 3 counties may have biased the study sample. Because participants self-selected into the study, we could not rule out the possibility of disproportionately excluding individuals who might have feared disclosure of socially undesirable behaviors such as injection drug use or MSM behaviors. This was corroborated by the fact that no HIV seroconversions were found to be attributable to injection drug use. Lastly, HIV incidence may have been overestimated due to the disproportionate loss to follow-up among the younger participants. Findings may not be representative of rural Southwest China.

To our knowledge, this is the first large-scale population-based prospective follow-up cohort study in China to evaluate HIV incidence among the general population. Study results provide compelling evidence that current HIV prevention intervention strategies designed primarily for key populations may be insufficient for addressing HIV transmission among the older, general population. It is incumbent for health authorities in China to develop and implement innovative interventions suitable for the broader population of older heterosexuals.

Older heterosexual males were at disproportionate risk of HIV infection in southwestern China, especially older heterosexual males who were single, divorced or widowed. Targeted interventions are urgently needed for this population. Health authorities in China need to develop and implement innovative interventions suitable for addressing HIV transmission among the older, general population.

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