


BMJ Open Increased kidney disease mortality among people with AIDS versus the general population: a population-based cohort study in Italy, 2006–2018

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ABSTRACT

Objectives This study aimed to assess whether an excess mortality related to kidney and other urinary tract diseases exists among Italian people with AIDS (PWA), as compared with the general population without AIDS (non-PWA).

Design Population-based, retrospective cohort study.

Setting and participants We conducted a nationwide study including 9481 Italian PWA, aged 15–74 years, reported to the National AIDS Registry between 2006 and 2018.

Methods Vital status and causes of death were retrieved by record linkage with the National Register of Causes of Death up to 2018. Excess mortality for PWA versus non-PWA was estimated through sex-standardised and age-standardised mortality ratios (SMRs) with corresponding 95% CIs.

Results Among 2613 deceased PWA, 262 (10.0%) reported at least one urinary tract disease at death, including 254 (9.7%) non-cancer diseases—mostly renal failures (225 cases, 8.6%)—and 9 cancers (0.3%). The overall SMR for non-cancer urinary tract diseases was 15.3 (95% CI 13.4 to 17.3) with statistically significant SMRs for acute (SMR=22.3, 95% CI 18.0 to 27.4), chronic (SMR=8.4, 95% CI 6.0 to 11.3), and unspecified renal failure (SMR=13.8, 95% CI 11.2 to 16.8). No statistically significant excess mortality was detected for urinary tract cancers (SMR=1.7, 95% CI 0.8 to 3.3). The SMRs were particularly elevated among PWA aged <50 years, injecting drug users, or those with the first HIV-positive test >6 months before AIDS diagnosis.

Conclusions The excess mortality related to non-cancer kidney and other urinary tract diseases reported among PWA highlights the importance of implementing the recommendation for screening, diagnosis and management of such conditions among this population.

INTRODUCTION

In developed countries, the cohort of people living with HIV is ageing, as a consequence of the longer life expectancy granted by highly active antiretroviral treatment (HAART).¹ Concurrently, the burden of disease not directly related to HIV/AIDS in this

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The high sensitivity of the validated record-linkage procedure limited the number of losses to follow-up.
- ⇒ The completeness of data sources with full coverage of the Italian population allowed robust comparisons between people with AIDS (PWA) and the general population.
- ⇒ The use of multiple cause of death data allowed to identify diseases that, otherwise, would have been hidden by the use of the underlying cause-of-death among people with HIV/AIDS.
- ⇒ Interpretation of study findings should take into account the absence of data on HIV-infected people without AIDS.
- ⇒ The lack of information about some risk factors for kidney diseases (eg, hepatic viral infections, alcohol abuse) did not allow to disentangle their effect on the mortality of PWA.

population is growing. Specifically, the contribution of non-infectious diseases (including cancers, cardiovascular, liver and kidney diseases) to the mortality of HIV-infected patients is becoming noteworthy.^{2–13}

Kidney diseases are clinically significant non-infectious comorbidities among people living with HIV due to their high morbidity and mortality.^{14 15} The constellation of HIV-associated nephropathies has been described in detail by Cohen *et al*.¹⁶ A recent large study has shown increased risks of hospitalisation for several kidney diseases among people with HIV as compared with the general population.¹⁷ Nevertheless, a lesser amount of evidence has been accumulated on the role of kidney diseases on the mortality of HIV-infected individuals as compared with the general population. Whiteside *et al*⁸ reported a more than double relative risk of death among HIV-positive people as compared with the general US population as of 2011. To the

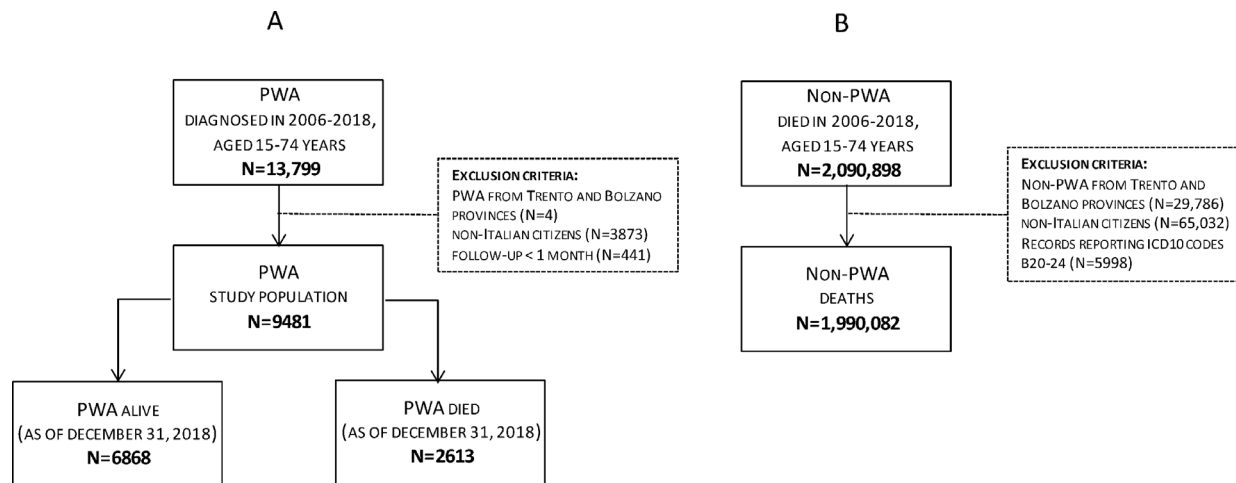


Figure 1 Flow chart of the (A) PWA and (B) non-PWA deaths. PWA, people with AIDS.

best of our knowledge, no other investigation has yet focused on this topic.

In order to further explore whether AIDS is associated with an excess mortality associated with kidney and other urinary tract diseases, we compared the mortality patterns of Italian people with AIDS (PWA) versus the Italian population without AIDS (non-PWA).

MATERIALS AND METHODS

We conducted a nationwide, population-based, retrospective cohort study. This study is part of an ongoing investigation on the mortality burden of Italian PWA¹⁸ that was included in the Italian National Statistical Plan, after clearance by the Italian Data Protection Authority. The study is based on the availability of two registries with nationwide coverage: (1) the National AIDS Registry (RAIDS)—to which all people newly diagnosed with AIDS in Italy must be reported by law; and (2) the National Register of Causes of Death (RCoD)—to which all death certificates issued in Italy must be referred by law.¹⁹

The RAIDS includes data on people diagnosed with AIDS according to the 1993 revised European definition²⁰; that is, it does not include HIV-positive individuals without an AIDS-defining disease. In particular, RAIDS includes demographic information on date of AIDS diagnosis, sex, age at diagnosis, date and place of birth, and residence at diagnosis; conversely, date of death is not mandatorily updated. The RCoD includes both the underlying cause of death (ie, the disease or injury which initiated the train of events leading directly to death) and the multiple cause of death (MCoD) data (ie, all diseases that the certifying physician considered relevant to death and thus are listed on the death certificate), according to the International Classification of Diseases 10th revision (ICD-10).

We defined as ‘late testers’ individuals whose AIDS diagnosis was made ≤ 6 months from first HIV-positive testing, and as ‘early testers’ those whose AIDS diagnosis was made > 6 months from first HIV-positive testing.

Record linkage

In order to retrieve the information on the causes of death of PWA, a record-linkage procedure was performed between the RAIDS and RCoD for the period 2006–2018. The record linkage was carried out using a semiautomated software application that was previously designed and validated in Italy, as described in detail elsewhere.²¹ This software application guarantees anonymity through a blinded procedure that was shown to have an elevated sensitivity ($> 95\%$).²² Briefly, the deterministic record-linkage procedure uses name, surname and date of birth as matching criteria, but name and surnames are blinded to the operator and encrypted in the output database. The automatic procedure tolerates common spelling errors in names/surnames and dates, thus producing both correctly (true positives) and incorrectly matched records (false positives). The false positives are then manually excluded by comparing the other variables present in both the original databases (eg, sex, place of birth). We excluded from the study the PWA from Trento and Bolzano ($n=4$), as these two provinces do not provide names and surnames to the RCoD. In order to reduce selection bias, we also excluded non-Italian citizens ($n=3873$), as their names/surnames are more frequently reported with complex spelling errors and they have a higher probability of dying abroad and, thus, they are not reported to the RCoD.

At the end of the record-linkage procedure, ‘PWA deaths’ were defined as the correctly matched records between RAIDS and RCoD, whereas, ‘non-PWA deaths’ were defined as the records in RCoD that were not linked to the RAIDS (ie, deaths of people without AIDS in the general population). From this latter group, we excluded records reporting any HIV/AIDS-mention in the death certificate (ie, ICD-10 codes B20–B24), in order to also avoid the inclusion of HIV-infected people among ‘non-PWA deaths’. For this study we restricted the analyses to PWA between 15 and 74 years of age at AIDS diagnosis and at death. We excluded PWA with a follow-up less than

Table 1 Distribution of 9481 Italian people with AIDS (PWA) and of 2613 PWA who died between the ages of 15 and 74 years, by selected characteristics, Italy, 2006–2018

Characteristics	Total PWA	PWA deaths*	
	N=9481	N=2613	
	No. (%)	No.	% died
Follow-up (years)			
Median (IQR)	5.4 (1.6–9.4)	0.6 (0.2–2.7)	
Total person years	53205	5143	
Sex			
Male	7696 (81.2)	2117	27.5
Female	1785 (18.8)	496	27.8
Age at AIDS diagnosis (years)			
15–39	2544 (26.8)	436	17.1
40–49	3753 (39.6)	1077	28.7
50–59	2167 (22.9)	705	32.5
60–74	1017 (10.7)	395	38.8
Calendar year at AIDS diagnosis			
2006–2009	3894 (41.1)	1367	35.1
2010–2013	2855 (30.1)	795	27.8
2014–2018	2732 (28.8)	451	16.5
HIV transmission mode			
Heterosexual intercourse	3621 (38.2)	888	24.5
MSM	2745 (28.9)	528	19.2
IDU	2215 (23.4)	950	42.9
Other/undetermined	900 (9.5)	247	27.4
Timing of first HIV+testing†			
Early testers (>6 months)‡	3452 (39.8)	1235	35.8
Late testers (≤6 months)§	5232 (60.2)	1133	21.7

*Up to 31 December 2018.
 †The sum does not add up to the total because of missing values.
 ‡PWA whose AIDS diagnosis was made >6 months from first HIV+testing.
 §PWA whose AIDS diagnosis was made ≤6 months from first HIV+testing.
 IDU, injecting drug use; MSM, men having sex with men.

1 month from AIDS diagnosis (n=441) as the day of AIDS diagnosis was frequently missing and AIDS could have been diagnosed as a consequence of death. Thus, the final study population consisted of 9481 PWA, 2613 ‘PWA deaths’ (figure 1A). The comparison group consisted of 1 990 082 ‘non-PWA deaths’ (figure 1B).

Patient and public involvement

No patient involved.

Statistical analysis

The excess mortality risks related to selected diseases were estimated by means of sex-standardised and age-standardised mortality ratios (SMRs), with the corresponding 95% CIs calculated using the exact Poisson method. SMRs were computed by dividing the observed number of ‘PWA deaths’ reporting specific diseases at

death—among MCoD—to the expected number of ‘PWA deaths’. The latter number was estimated by multiplying the sex-specific and age-specific person years at risk of death among PWA by the sex-specific and age-specific mortality rates among ‘non-PWA deaths’. The person years among PWA were calculated by summing up the years from the date of AIDS diagnosis to the date of death, or to 31 December 2018, whichever came first; those diagnosed with AIDS before 75 years of age who died subsequently were censored at the date of their 75th birthday. Sex-specific and age-specific person years took account of the age change during the follow-up period (ie, each PWA can contribute person time in different age groups). Sex-specific and age-specific mortality rates were computed by dividing the number of ‘non-PWA deaths’ reporting the same specific diseases at death—among MCoD—to the average resident Italian population in the same calendar period, of same sex and quinquennium of age (from 15–19-year age group to 70–74-year age group, excluding Trento and Bolzano provinces and foreign citizens), as a proxy of person years at risk of death among non-PWA. The detailed calculation of the SMRs is provided in online supplemental table 1.

RESULTS

The 9481 Italian PWA aged 15–74 years and diagnosed during 2006–2018 were followed up for a total of 53 205 person years, with a median follow-up time of 5.4 years (IQR 1.6–9.4 years) (table 1).

Overall, 2613 PWA (27.6%) died between 15 and 74 years of age during the study period; the follow-up time had a median of 0.6 years (IQR 0.2–2.7 years) and was right tailed. The main HIV transmission mode was heterosexual intercourse (38.2%), and the majority of PWA (60.2%) consisted of ‘late testers’ (ie, ≤6 months between the first HIV+testing and AIDS diagnosis). The proportion of deaths among PWA was approximately 28% in both sexes, increased with age at AIDS diagnosis up to 38.8% among those aged 60–74 years, and was higher (42.9%) among injecting drug users (IDUs), and among ‘early testers’ (35.8%).

Table 2 shows the observed number of death certificates reporting urinary tract diseases among PWA, the expected number of deaths, and the corresponding SMRs.

Overall, 262 (10.0% out of 2613) of PWA death certificates reported at least one urinary tract disease (table 2). Among these, urinary tract cancers were mentioned in just 9 cases (0.3%), whereas 254 (9.7%) were non-cancer diseases, mostly including renal failure (225 cases, 8.6%). When considering all urinary tract conditions, a 12.5-fold excess mortality was found among PWA as compared with non-PWA (95% CI 11.0 to 14.1) (table 2). Statistically significant excess risk of death emerged for all non-cancer urinary tract diseases (SMR=15.3, 95% CI 13.4 to 17.3), including glomerular diseases (SMR=44.8, 95% CI 20.5 to 85.0), renal tubulointerstitial diseases (SMR=22.2, 95% CI 8.9 to 45.8), acute (SMR=22.3, 95% CI 18.0 to

Table 2 Standardised mortality ratios and corresponding 95% CIs according to selected causes of death reported in death certificates of people with AIDS (PWA), versus people without HIV/AIDS, Italy, 15–74-year PWA, 2006–2018

Causes of death (ICD-10 codes)*	PWA deaths (N=2613)		
	Observed no. of deaths (%)	Expected no. of deaths	SMR (95% CI)
Urinary tract diseases (C64–C68, D09.0, D30.3, D41.4, N00–N39)	262 (10.0)	21.0	12.5 (11.0 to 14.1)
Urinary tract cancers (C64–C68, D09.0, D30.3, D41.4)†	9 (0.3)	5.2	1.7 (0.8 to 3.3)
Kidney (C64)	5 (0.2)	2.3	2.2 (0.7 to 5.1)
Bladder (C67, D09.0, D30.3, D41.4)	3 (0.1)	2.5	1.2 (0.2 to 3.5)
Urinary tract non-cancer diseases (N00–N39)	254 (9.7)	16.6	15.3 (13.4 to 17.3)
Glomerular diseases (N00–N08)	9 (0.3)	0.2	44.8 (20.5 to 85.0)
Tubulointerstitial diseases (N10–N16)	7 (0.3)	0.3	22.2 (8.9 to 45.8)
Renal failure (N17–N19)	225 (8.6)	15.2	14.8 (12.9 to 16.8)
Acute (N17)	92 (3.5)	4.1	22.3 (18.0 to 27.4)
Chronic (N18)	42 (1.6)	5.0	8.4 (6.0 to 11.3)
Unspecified (N19)	101 (3.9)	7.3	13.8 (11.2 to 16.8)
Other urinary tract non-cancer diseases (N20–N39)	29 (1.1)	1.8	16.2 (10.8 to 23.2)

*Using the multiple cause of death data (ie, each death certificate can report more than one cause), the sums can exceed the total. Causes of death reported in the same death certificate within the same ICD-10 group were counted only once.

†It includes one case of malignant neoplasm of other and unspecified urinary organs (ICD-10 code: C68).
ICD-10, International Classification of Diseases 10th revision; SMR, standardised mortality ratio.

27.4), chronic (SMR=8.4, 95% CI 6.0 to 11.3), and unspecified renal failure (SMR=13.8, 95% CI 11.2 to 16.8), and other urinary diseases (SMR=16.2, 95% CI 10.8 to 23.2). Considering all urinary tract cancers combined, a slightly elevated, though not statistically significant, excess mortality was found among PWA (SMR=1.7, 95% CI 0.8 to 3.3), and this seemed mainly driven by kidney cancers (SMR=2.2, 95% CI 0.7 to 5.1). When considering strata of PWA (online supplemental table 2), the SMRs were particularly elevated among PWA who died at a younger age (figure 2A) and particularly among women: among PWA aged 15–49 years, SMRs were 64.7 (95% CI 41.9 to 95.5) in women and 36.8 (95% CI 29.2 to 45.7) in men;

among those aged 50–74 years, SMRs were 11.4 (95% CI 6.5 to 18.5) in women and 8.2 (95% CI 6.9 to 9.7) in men (data not shown). Furthermore, particularly elevated SMRs emerged among IDUs (figure 2B), and among ‘early testers’ (figure 2C).

When analysing the coexisting presence of urinary tract diseases and other conditions in death certificates, we found elevated frequencies of circulatory system diseases (27.5%), viral hepatitis (22.5%), AIDS-defining cancers (22.1%), non-AIDS-defining cancers (12.2%) and diabetes mellitus (6.5%) (table 3).

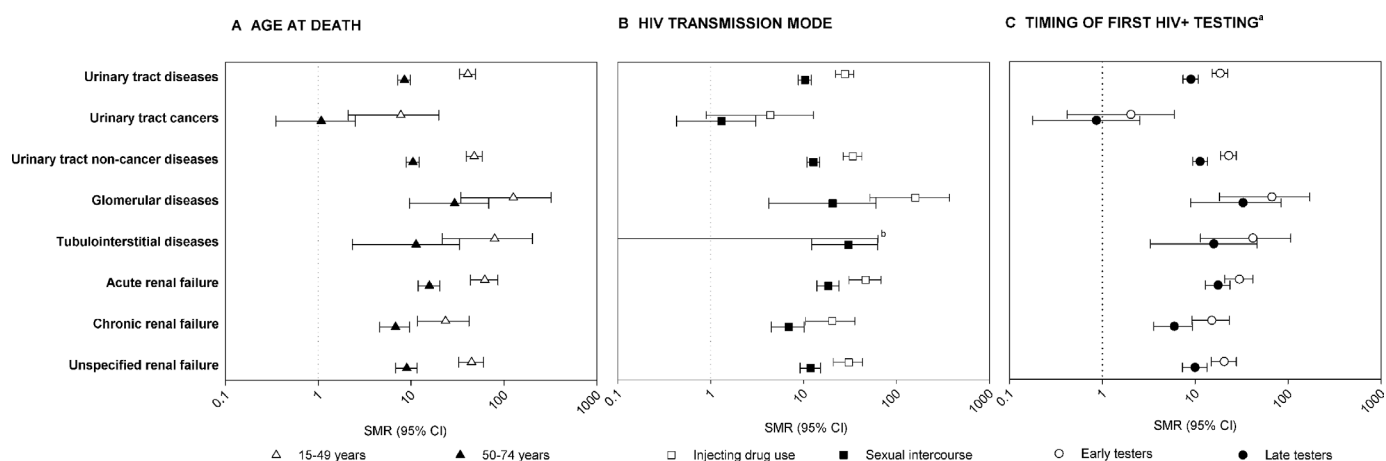


Figure 2 Standardised mortality ratios (SMR) and corresponding 95% CIs according to selected causes of death reported in death certificates of people with AIDS (PWA), as compared with people without HIV/AIDS, by age at death (A), mode of HIV transmission (B), and timing of first HIV+testing (C). Italy, 15–74-year PWA, 2006–2018. ^a‘Early testers’: PWA whose AIDS diagnosis was made >6 months from first HIV+testing. ‘Late testers’: PWA whose AIDS diagnosis was made ≤6 months from first HIV+testing. ^bNo observed cases among PWA.

Table 3 Leading causes of death recorded together with urinary conditions in death certificates of people with AIDS (PWA), Italy, 15–74-year PWA, 2006–2018

Causes of death (ICD-10 codes)	PWA with urinary conditions in death certificates
	(N=262)
	No. (%)
Circulatory system diseases (I00–I99)*	72 (27.5)
Hypertension (I10–I15)	15 (5.7)
Ischaemic heart diseases (I20–I25)	13 (5.0)
Other forms of heart disease (I30–I52)*	31 (11.8)
Cerebrovascular diseases (I60–I69)	16 (6.1)
Diabetes mellitus (E10–E14)	17 (6.5)
Viral hepatitis (B15–B19)	59 (22.5)
Cancers other than urinary tract (C00–C63, C69–C99)†	89 (34.0)
AIDS-defining	58 (22.1)
Kaposi's sarcoma (C46)	19 (7.3)
Non-Hodgkin's lymphoma (C82–C85, C96)	40 (15.3)
Non-AIDS-defining†	32 (12.2)

*Except I46 (ie, cardiac arrest).
 †Except C77–80 (ie, secondary malignant neoplasms or unspecified cancers).
 ICD-10, International Classification of Diseases 10th revision.

DISCUSSION

This nationwide, population-based study found an excess of mortality among Italian PWA, as compared with non-PWA, related to non-cancer urinary tract diseases, in particular, acute, chronic and unspecified renal failures. Conversely, no excess death risk was detected for urinary tract cancers. Nonetheless, an indication of possible higher mortality emerged for kidney cancer, although our study did not have sufficient statistical power to detect a significant SMR due to the very low number of observed events (n=5).

The pattern of kidney diseases among people with HIV has changed after the introduction of HAART, both in the USA and Europe, shifting from infection-related (such as the HIV-associated nephropathy) to chronic comorbidities and nephrotoxicity associated with HAART use.²³ Indeed, the prolonged exposure to HAART and other medical therapies for HIV-related infections can lead to a wide variety of nephrotoxic effects.¹⁴ Although HAART has changed the natural course of HIV-associated nephropathy, reducing the risk of end-stage renal disease, some antiretroviral regimens have been associated with the development of acute and chronic kidney diseases.^{24,25}

In this study, we could not directly evaluate the contribution of HAART to the onset of kidney diseases, as information on treatments following AIDS diagnosis was not available in the RAIDS. To this regard, it should be noted that in Italy, thanks to the presence of a universal health-care system, all HIV-positive individuals who present for treatment have complimentary access to HAART. However, our cohort of PWA mostly consisted of people with a short time interval between the first HIV-positive

test and AIDS diagnosis (ie, late testers) who, probably, had never been treated with HAART. Indeed, in the stratified analyses, we found particularly elevated SMRs among 'early testers' who, conversely, almost certainly underwent HAART and could have been affected by the nephrotoxic effects of antiviral treatments.²⁶

Our findings reflect the increased incidence of kidney diseases among HIV-infected people compared with non-HIV-infected.¹⁷ An observational nationwide French study reported a 1.5-fold higher prevalence of kidney diseases among hospitalised people with HIV than in the general population, with an increasing trend over time.¹⁷ The main cause of hospitalisation was acute kidney injury (25%), which in that study included also unspecified renal failure.

Chronic kidney disease has been indicated as one of the most relevant non-communicable disease affecting people with HIV, reporting also an increasing prevalence.¹⁴ Chronic kidney disease has been shown to be often related to not only non-infectious comorbidities, particularly diabetes mellitus and hypertension, but also hepatitis C.¹⁴ This study found that circulatory system diseases and viral hepatitis were present as coexisting conditions with kidney diseases in half the PWA death certificates stating urinary conditions, while diabetes mellitus was less frequent. In a previous paper, we have already shown an excess mortality related to diabetes and circulatory system diseases, including hypertension,¹² and viral hepatitis¹³ among Italian PWA.

Unhealthy lifestyles, including smoking, drugs and alcohol abuse, and sexually-acquired viral infections (such as HBV and HCV), are more common among HIV-infected individuals than among the general population.^{2,6} Therefore, they can be partly responsible for the excess mortality related to urinary tract diseases reported in our investigation, especially among PWA who acquired HIV via injecting drug use, who are also generally affected by other comorbidities. However, we could not analyse the contribution of these factors, as they are available neither in RAIDS, nor in RCoD database. Further, the higher SMR found among people aged 15–49 years, as compared with the older age group, may be attributable to the high proportion of IDUs (39%) among 106 PWA deceased for urinary diseases at a younger age, or it may merely be a numerical effect related to the very low death rates among non-PWA in this age group.

Regarding urinary cancers, previous investigations have suggested that the risk of kidney cancer, particularly renal cell carcinoma, is modestly high among HIV-infected individuals and that its incidence may increase over time.²⁷ Although limited data are available on bladder cancer among HIV-infected people, the risk of this cancer appears to be lower in HIV-infected subjects compared with the general population and this is somewhat surprising given the high rate of smokers in this population.²⁷ In line with other recent studies^{28–30} and with our previous investigation conducted on non-AIDS-defining cancers¹⁰ no augmented risks were observed for

bladder or kidney cancers. Nevertheless, to draw firm conclusions, a larger number of cases are needed.

This study further highlighted the importance of using MCoD data in evaluating the mortality of people infected with HIV, as these data allow to disclose the contribution to death of conditions other than directly AIDS-related ones. In this study, out of 262 PWA deaths for whom a urinary tract disease was reported among the MCoD, 187 (71.4%) deaths certificates stated HIV/AIDS as the underlying cause of death, 65 (24.8%) other causes, and only 10 (3.8%) urinary conditions (data not shown).

Among the strengths of our investigation, the use of MCoD allowed consideration of the contribution to death of all conditions that the certifying physician considered relevant to the death - thus worthy of being listed on the death certificate, overcoming the limitation deriving from the assignment of HIV/AIDS as the underlying cause-of-death to most people with HIV/AIDS, according to official statistics rules.^{3,11} Furthermore, the use of MCoD data for both PWA and non-PWA granted the use of the same coding rules for both groups, thus limiting information bias. The average number of causes of death mentioned in the death certificates of people with and without AIDS was similar (5.3 and 4.1, respectively), considering the additional presence of HIV/AIDS for PWA. Nevertheless, we cannot exclude that the knowledge of AIDS could have influenced the notification of other diseases in the death certificate.

Additional relevant strengths of this study are the national coverage of the Italian population for both RAIDS and RCoD registries and the high sensitivity of the record-linkage procedure used.^{21,22} However, the inclusion of PWA and not all HIV-infected people represents a limitation. Therefore, it should be stressed that our findings cannot be extended to people at an earlier stage of infection, as they were obtained from the RAIDS, which does not include HIV-positive people without AIDS-defining diseases (HIV only). Consequently, the SMRs may be different in the case of HIV-only people for whom the competitive role of AIDS-defining diseases at death should be null. Finally, although it is known that in Italy HAART therapy began in 1996, and since 2000 it was adopted in all Italian clinical centres, in the RAIDS data on post-AIDS use of HAART are not available, which represents another important limitation. As a consequence, the contribution of HAART to the onset of kidney diseases could not be evaluated.

Our nationwide, population-based study showed an excess mortality related to several types of kidney and urinary tract diseases among Italian PWA, as compared with the general population without HIV/AIDS. These results highlight the importance of preventive actions, especially among younger patients and those injecting drugs. Moreover, it is crucial to assess the renal function at baseline before HAART initiation and to periodically monitor the renal function in patients with HIV. Recommendations for kidney disease screening, diagnosis and management specifically targeted to HIV-infected

individuals have been defined in recent years by an international panel of experts³¹ and they should be implemented in the clinical practice.

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Contributors AZ and BS designed the study. MT performed the statistical analyses. AZ, MT, BS and DS drafted the manuscript. VR and LP managed the National AIDS Registry data used in this study. LF, EG, FG and MP managed data of the National Register of Causes of Death used in this study. AZ, FT and MT performed the record linkage between National AIDS Registry and National Registry of Causes of Death and managed the final database. All authors revised the study results, contributed to data interpretation, reviewed the draft of the manuscript, and approved the final version of the manuscript. MT is responsible for the overall content as guarantor.

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