

ORIGINAL RESEARCH

The incidence of cardiovascular disease, cancer and type 2 diabetes comorbidities in HIV infection: A systematic review

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Abstract

Introduction: Epidemiological linkages between HIV/AIDS and common Noncommunicable diseases are established. However, the incidence of these diseases among people living with HIV is not well examined.

Objectives: To describe the incidence of cardiovascular diseases, cancers, and type 2 diabetes among people living with HIV.

Methods: We have conducted a systematic review of incidence studies. Studies reporting on the incidence of cardiovascular diseases, cancers and type 2 diabetes among People living with HIV were retrieved from Embase and Medline databases. We used explicit eligibility and quality appraisal criteria to screen and select studies. We extracted study characteristics, outcome values and key conclusions. Findings were reported using tables and narrative summaries.

Results: A total of 30 studies were included in this systematic review. The incidence of cardiovascular diseases, cancers, and type 2 Diabetes comorbidities among people living with HIV was found to range from 1.19 to 11.3, 6.63 to 43.77, and 4.42 to 36.26 per 1000 person years, respectively. HIV infection was associated with increased risk of cardiovascular diseases and cancers. Specific types of antiretroviral drugs and longer duration of antiretroviral treatment were among the determinants of cardiovascular diseases and type 2 Diabetes in HIV infection. While the introduction of antiretroviral treatment was followed by a rapid decline in the incidence of AIDS-defining cancers, its effect on the incidence of non-AIDS defining cancers looks minimal.

Conclusion: The current evidence suggests that policies and interventions targeting people living with HIV should prioritize the prevention of the risk of common Noncommunicable diseases together with the rapid scale up of HIV treatment.

Key words

HIV-NCD comorbidity, Magnitude, Incidence

1 Introduction

The epidemiological transition towards double-burden of diseases is expected to result in higher rates of comorbidity^[1]. It is generally well understood that some infectious diseases are associated with increased risk of Non-communicable diseases (NCDs). On the other hand, NCDs predispose people to opportunistic infectious diseases^[2]. Furthermore, some infectious diseases affect the risk of contracting other infectious diseases resulting in greater co-infection rates^[3]. This also applies for NCDs. Hence, the relationships between and within disease categories are so complex but are worth considering. These complexities manifest as comorbidity.

There is no single agreed up on definition of comorbidity. Comorbidity may refer to diseases or disorders that exist together with an index disease; or it may refer to the co-occurrence of two or more diseases in an individual. Measurement of comorbidity has currently received more attention in medical research. Different data sources that are available to measure comorbidity include medical records, patient self-report, clinical judgment and administrative databases. Comorbidity can assume four major roles in statistical analysis: a confounder, an effect modifier, an exposure and an outcome. Most comorbidity studies involve the development and application of comorbidity indices to understand the effect of comorbidities on defined health outcomes^[4-6].

NCD comorbidity in HIV infection, the occurrence of an NCD in an individual with HIV, currently requires more attention along with the rapid emergence of NCDs as a major disease of public health importance in high HIV prevalent areas. Low-and-middle income countries which already have high magnitude of HIV are expected to share high burden of NCD comorbidity due to the associated increase in the incidence of NCDs^[7].

Though more is known about the clinical relationship between HIV and NCDs and the factors associated with their relationship, little is known about the epidemiology of their comorbidity. With the emergence of double mortality burden in low-and-middle income countries, better understanding of the epidemiology of HIV-NCD comorbidity is essential^[8]. Data on the incidence and prevalence of common NCDs among people with HIV are available from different studies in different parts of the world. There are also several studies that have reported the effect of antiretroviral treatment on the risk of developing NCDs among people living with HIV (PLHIV). However, to the knowledge of the investigators, there is no research effort that summarizes the incidence of comorbidities of common NCDs in HIV infection.

Therefore, the aim of this study was to review and summarize the incidence of comorbidities of the cardiovascular diseases, cancers, and Diabetes and to describe the determinants of incidence of these comorbidities among people living with HIV.

2 Methods

2.1 Search strategy and selection

Studies reporting the incidence of cardiovascular disease, cancer and type 2 diabetes comorbidities among people living with HIV/AIDS were retrieved from Embase and Medline electronic databases. The key words used contain HIV/AIDS, one NCD term and incidence. The search was then filtered for cohort studies and registry matches only. References of review articles^[9-12] were also assessed to identify additional studies. The titles and abstracts of the resulting studies were reviewed for eligibility. The eligibility criteria used were: 1) Studies that report incidence of cardiovascular diseases (CVD), cancers or diabetes; 2) Studies mainly conducted on people living with HIV; and 3) published between 2000 and 2012. Studies that meet all these eligibility criteria were considered for review.

2.2 Appraisal of the studies

We assessed all the eligible studies for the following appraisal criteria: 1) clearly defined cohort study design or registry match; 2) Sufficient sample size (more than 500 PLHIV); 3) Adequate follow up period (at least one year); 4) assessment at index visit and appropriate outcome ascertainment stated; and 5) explicitly stated comparison group including self (time- series) comparison. These criteria were rated on a dichotomous scale (1=Yes and 0=No). Studies that met all these criteria were included in the final review. In those cases where more than one study reported from the same cohort met the appraisal criteria, the most recent study was included.

2.3 Data extraction

We extracted relevant study and outcome characteristics using a standardized checklist. This checklist was pre-tested on 5 studies before application. Necessary amendments were made based on the results of the pre-test. The information extracted include name of first author, year of publication, study design, study population characteristics, follow up period, sample size for PLHIV, country of the study, number of new cases, total person-years of follow, incidence rates, associated risk factors, measures of association and major conclusion of the study. All these variables were double entered independently to ensure consistency of the extraction.

2.4 Synthesis techniques

Incidences of comorbidities were examined among studies within each NCD and among the three common NCDs. The findings were discussed based on the characteristics of the studies and the relative magnitude of the NCDs. Meta-analytic combination of findings was precluded by high level of heterogeneity among the studies. Even though confidence intervals of the incidence rates were recalculated from the available information, these were used for descriptive purpose only. For three studies person-years of follow up was estimated from average duration of follow up. Key findings of the studies that compared the incidence of the comorbidities of the three NCDs between 1) PLHIV (not on ART) versus HIV uninfected; 2) PLHIV (on ART) versus HIV uninfected; 3) PLHIV on ART versus PLHIV not on ART; and 4) PLHIV treatment groups (by type of drug and by duration of treatment) were also highlighted. Findings were reported using PRISMA guideline^[13].

3 Results

3.1 Study characteristics

The search strategy had resulted in a total of 533 studies. Ninety eight studies met the initial eligibility criteria. Full texts of these 98 studies were retrieved and reviewed. A total of 30 studies had met the quality appraisal criteria and were included in the final review (see Table 1).

Table 1. Number of studies addressing incidence of NCD comorbidities in HIV

S#	Type of NCD	Screened	Eligible	Included
1	Cardiovascular disease	274	22	10
2	Cancers	176	50	14
3	Type 2 diabetes	83	26	6
	Total	533	98	30

The majority of the included studies were conducted in USA. All the included studies were conducted in the developed world, i.e. USA, Europe and Australia. Most of the studies that had reported incidence of cancer was registry match studies while most of the studies that had reported incidences of CVD and Diabetes were prospective cohort studies. Most of the

studies that had reported incidence of cancer were published between 2000 and 2005 while most of the studies that had reported the incidence of CVD and Diabetes were published after 2005.

3.2 Cardiovascular diseases (n=10)

A total of 186,867 people living with HIV were followed for about 705,772 person-years. During this follow up period a total of 1,654 new cases of cardiovascular disease were identified. From the included studies the incidence of CVD among PLHIV ranges from 1.19 to 11.13 per 1000 person-years of follow up (see Table 2).

Table 2. Cohort studies reporting the incidence of CVD among HIV infected people

Author	Year	Follow up period	PLHIV	New CVD cases	Person years	Incidence [#] (HIV+)	Country
Lang S ^[14]	2010	2000-2006	74958	360	298156	1.24	France
Triant VA ^[15]	2007	1996-2004	3851	189	16983	11.13	US
Klein ^[16]	2007	2000-2006	6702	95	25200	2.40	US
Holmberg ^[17]	2002	1993-2002	5672	21	17712*	1.19	US
Mary-Krause ^[18]	2003	1996-1999	34956	60	88029	4.90	France
Iloeje ^[19]	2005	1996-2003	7542	127	23765*	5.34	US
SMART ^[20]	2008	2004-2007	2752	112	26047*	4.30	UK, Den, AU.
Brothers ^[21]	2009	1997-2004	14174	43	11921	3.61	US
Worm S ^[22]	2010	1999-2007	33308	580	178835	3.24	US, EU, AU
Obel N ^[23]	2010	1995-2005	2952	67	19124	3.50	Denmark

#Per 1000 person years of follow up; *Estimated from average duration of follow up and incidence rates; US=United States; UK=United Kingdom; EU=Europe; AU=Australia

Studies included in this review indicated that HIV-positive people have increased risk of cardiovascular disease as compared to HIV-negative people. The risk of myocardial infarction among people living with HIV was about 1.5 times that of HIV negative people^[14]. In comparison to other cardiovascular diseases, the relative risk of acute myocardial infarction was higher at about 1.75 times that of HIV-negative people^[15]. The risk of coronary heart disease was also about 1.78 times more among PLHIV in late HAART^[16].

Studies had also indicated that the risk of CVD among PLHIV taking Antiretroviral treatment (ART) depends on the specific type of the Antiretroviral drug used. Holmberg et al had found that the hazard ratio of myocardial infarction among PLHIV who were taking Protease inhibitors was about 6.5 (95% CI: 0.9-47.8) times as compared to its hazard ratio among those who were not taking protease inhibitors^[17]. Compared to treatment naïve PLHIV, PLHIV taking Protease inhibitors had about 2.56 (1.03, 6.34) times more risk of myocardial infarction^[18]. Although statistically significant, the findings from a study by Iloeje et al indicated modest level of risk of CVD associated with Protease inhibitor use, a Hazard ratio of 1.71 (1.08, 2.74) as compared to Non-Protease inhibitor users^[19]. PLHIV taking abacavir containing ART were about 2 times at a higher risk of CVD as compared to those taking other regimens that do not containing this drug^[20]. However, the study by Brothers et al reported no supportive evidence of increased risk of CVD among Abacavir users^[21].

Other studies from the D: A: D cohort indicated that both Abacavir and Didanosine use were associated with about 2 times increased risk of Myocardial infarction as compared to other antiretroviral drugs^[24]. From the same cohort, it was reported that the duration of exposure to ART was also a factor for increased risk of CVD. A study from D: A: D showed that ART was independently associated with a 26% relative increase in the rate of Myocardial Infarction per year of exposure during the first four to six years of its use^[25].

3.3 Cancers (n=14)

Fourteen studies that had reported the incidence of cancers among PLHIV were reviewed. Most of the studies used registry match as their major method of identifying HIV cases with cancer. The others were prospective cohort studies. The incidence rate of cancer ranged from 6.63 to 43.77 per 1000 person years of follow up. Overall, 84,374 cancers were reported in 3,422,910 person years of follow up. The majority (81.4%) of these were AIDS defining cancers (ADC). The rest 18.6% were non-AIDS defining cancers (NADC). High variations of among incidence rates were observed (see Table 3).

Table 3. Incidence rates of cancer (all types) per 1000 person years of follow up

Author (Ref)	Year	Follow up	PLHIV	Person years	Incidence (ADC)	Incidence (NADC)	Incidence (All)	Country
Frisch ^[26]	2001	1980-1996	302834	1438462	21.45	3.07	24.52	US
Glurich ^[27]	2002	1985-1999	13067	77114	5.72	2.54	8.26	Australia
Allardice ^[28]	2003	1981-1996	2754	15913	8.67	1.51	10.18	Scotland
Dal Maso ^[29]	2003	1985-1998	12104	60421	16.42	2.81	19.23	Italy
Clifford ^{[30]*}	2005	1985-2002	7304	28836	17.06	4.58	21.64	Switzerland
Newnham ^[31]	2005	1985-2001	33190	189758	8.33	2.33	10.66	UK
Engels ^[32]	2006	1980-2002	317428	477368	39.68	3.41	43.09	US
Mbulaiteye ^[33]	2003	1990-1996	82217	107728	40.44	3.33	43.77	US
Guiquet ^{[34]*}	2009	1998-2006	52278	255353	4.21	2.42	6.63	France
Patel ^{[35]*}	2008	1992-2003	54780	157819	4.49	18.01	22.49	US
Seaberg ^{[36]*}	2010	1984-2004	2940	32383	23.28	2.87	26.16	US
Glaceran ^[37]	2007	1981-1999	1659	7050	24.26	2.98	27.24	Spain
Bedimo ^{[38]*}	2004	1989-2002	2882	7452	23.89	6.58	30.46	US
Gallagher ^[39]	2001	1981-1994	122993	567254	14.13	8.25	22.39	US

*prospective cohort studies

The overall relative risk of NADC cancer was 2.7 (95% CI: 2.7-2.8) in Frisch et al study. But the incidence of NADC didn't appear to be influenced by advanced immunosuppression associated with HIV disease progression ^[26]. People with HIV who are only mildly immune deficient may not be at increased risk of NADC ^[27]. A study by Allardice et al, conducted before ART become widely available, had reported Standardized incidence ratio (SIR) of 10.8 (95% CI: 9.2-12.6) for all cancers. The SIR for NADC in this study was 1.8 (95% CI: 1.1-2.6) ^[28]. Another study conducted in Italy had reported SIR of 2.3 (95% CI: 2.0-2.7) for NADC. Anal cancer, lung cancer and brain tumours were among those NADCs with the highest SIR ^[29].

A study that examined the influence of behavioral risk factors and ART on the risk of cancer using data from the Swiss HIV cohort study didn't find any cancers of lip, mouth, pharynx and lung among non-smokers. This study had also suggested that ART may not prevent the risk of NADC ^[30]. A study conducted in Southeast England reported SIR of 2.8(95% CI: 2.6-3.1) for NADC. In this study men were at a higher risk of cancer ^[31]. A study that had investigated the effect of ART on cancer trend in US indicated that ART was associated with a dramatic decline in Kaposi Sarcoma and Non-Hodgkin Lymphoma. The risk of cervical cancer didn't change with ART. Decline in risk of lung cancer but an increase in risk of Hodgkin lymphoma was observed. No overall change in risk of NADC was associated with ART ^[32].

A study that examined the relationship between cancer risk and AIDS-related immunosuppression (as measured by CD4 count at AIDS onset) had illustrated that the risks of Kaposi Sarcoma and Non-Hodgkin Lymphoma were positively associated with CD4 count. However, the risks of cervical cancer and NADCs were not related to CD4 counts, suggesting

that increased risks of NADCs may be a result of lifestyle factors ^[33]. A prospective cohort study from France had also indicated that ART might be more beneficial the reducing the risk of cancer if it can restore or maintains CD4 count above 500 cells per micro litre, thereby indicating the need for an earlier diagnosis of HIV infection and an earlier treatment initiation ^[34].

A study on the incidence of cancer among HIV infected people as compared to the general population in the US reported that the incidence of many NADCs was higher among HIV infected persons ^[35]. In the multicentre AIDS cohort study among men, the incidence of Kaposi Sarcoma and Non-Hodgkin lymphoma has decreased while the incidence of anal cancer has increased in the HAART era as compared to the pre-HAART era ^[36]. Increased risks of Hodgkin's lymphoma, liver cancer, lung cancer, and in situ cervical cancer among AIDS patients were also reported by a study conducted in Spain ^[37]. A longer duration of survival during the HAART era was proposed to be one of the explanations for increased risk of NADC among PLHIV ^[38].

Elevated risks of Hodgkin's disease; cancer of rectal area, respiratory tract, brain and central nervous system were found in a study of AIDS patients in New York State. Increasing trends of increase relative risks from the pre-AIDS to the post-AIDS period were observed for cancers of the rectal and anal area, respiratory tract, skin, and connective tissues among men and invasive cervical cancer in women ^[39].

3.4 Diabetes (n=6)

Six prospective cohort studies that measured the incidence of diabetes among people living with HIV were included in this review. Three of these studies recruited PLHIV receiving treatment, treatment naive PLHIV and HIV-negative people in the follow up. One study recruited PLHIV receiving treatment and treatment naive PLHIV only. The rest three studies had focused on PLHIV taking ART only.

Over a total of 175,202 person-years of follow up 1,178 of the 44,484 HIV positive persons developed type 2 diabetes. The incidence of diabetes ranged from 4.42 cases per 1000 person years in Swiss HIV cohort study to 36.26 cases per 1000 person years in the multicenter AIDS cohort study. A study from the D: A: D cohort which had the highest number of study participants and person years of follow up had reported an incidence of 5.72 per 1000 person years (see Table 4).

Table 4. Incidence of Diabetes among PLHIV in the seven prospective cohort studies

Author	Year	Follow up period	Number of HIV+	New DM cases	Person years	Incidence [#] (HIV+)	Incidence [*] (ART users)
Capeau ^[40]	2012	2000-2009	1,046	111	7,846	14.18	14.18
De Witt ^[41]	2008	1999-2006	33,398	744	130,151	5.72	5.72
Justman ^[42]	2003	1994-1999	1,435	56	3,673	15.25	17.33
Brown ^[43]	2005	1999-2003	568	28	772.1	36.26	47.17
Ledergerber ^[44]	2007	2000-2006	6,513	123	27,798	4.42	4.99
Tein ^[45]	2007	2000-2006	1,524	116	4,962	23.37	27.36

[#]Studies conducted on ART users only

^{*}Incidence per 1000 person-years of follow up

Older age and adiposity were linked with higher risk of diabetes among PLHIV who had started on combination antiretroviral treatment at French clinical sites ^[40]. The use of two thymidine analogs (Stavudine and Zidovudine) was significantly associated with diabetes after the adjustment of potential confounders in a study reported from D: A: D cohort. In the same study, the incidence of diabetes was found to increase with cumulative exposure to combination antiretroviral treatment after adjustment for potential risk factors of diabetes ^[41].

Protease inhibitors use was found to be associated with a three-fold increase in the risk incident diabetes. Age and body mass index were also important predictors of risk of diabetes among PLHIV^[42]. In the Muticenter AIDS cohort study, the relative risk of diabetes among HIV infected men taking HAART was more than four times that of HIV sero-negative men after adjustment for age and body mass index^[43].

In a study reported from the Swiss HIV cohort, traditional risk factors, and current treatment with protease inhibitor- and nucleoside-reverse transcriptase- containing regimens were associated with risk of type 2 diabetes mellitus^[44].

In the women's interagency HIV cohort study, there was 1.4 fold increased incidence of diabetes in HIV infected women as compared to HIV negative women, but the difference was not statistically significant. This study had also reported a relative hazard of 2.64 [95% CI: 1.11-6.32] for the risk of diabetes among PLHIV who were exposed to Nucleoside reverse transcriptase for more than three years suggesting that longer exposure to Nucleoside reverse transcriptase inhibitors may increase risk of diabetes^[45].

4 Discussion

The incidence of CVD as reported by the studies included in this review was between 2.24 and 5.34 per 1000 person years except for one study which reported an incidence of 11.3 per 1000 person years and two studies which have reported incidence rates below 1.5 per 1000 person years. The higher incidence in Traint VA et al study could be due to the recruitment of older patients from a higher risk background population in tertiary hospitals^[15]. The incidence of CVD was relatively low in the two studies due to the low level of incidence of the problem in the background population^[14, 17].

The findings support the notion that HIV infection is generally associated with increased risk of cardiovascular disease. They are also in favor of the importance of antiretroviral treatment in decreasing the risk of cardiovascular diseases. However, the use of specific antiretroviral drugs is found to be associated with a higher risk of cardiovascular disease as compared to the use of other antiretroviral drugs.

The incidence of cancers was highly variable among the studies. The SIR of ADCs was very high while that of NADC was modest. Antiretroviral treatment was associated with a rapid decline in the incidence of ADCs. However, the effect of ART on the incidence of NADCs seems low. In some cases an increasing trend of NADC was observed among PLHIV receiving ART (36). Several body parts were found to be affected by NADCs. Longer survival and the role of traditional risk factors were also found to be more important.

The two largest studies reported the incidence of type 2 Diabetes among PLHIV to be 5.72 and 4.42 per 1000 person years^[41, 44]. The other studies have reported incidence rates of greater than 14 per 1000 person years. The risk of diabetes associated with antiretroviral use also varied by the type of the drugs considered. Protease inhibitors are associated with about 3 times increased risk of diabetes as compared to other types of drugs. Nucleoside reverse transcriptase inhibitors such as Stavudine, Didanosine, Zidovudine and Indinavir are also associated with increased risk of diabetes.

5 Limitations

We have encountered higher level of heterogeneity among the characteristics and outcomes of the included studies during the review. This had effect on the overall interpretation of the findings of the study. Besides, the number of studies that met the inclusion criteria for type 2 diabetes was low. The review had also looked in to cardiovascular and cancers in general terms and specific types of cardiovascular diseases and cancers are not well addressed by this review. Moreover, all the included studies were from the developed world and could not reflect the magnitude and determinants of major NCDs in high HIV prevalent areas of the developing world like Sub-Saharan Africa.

6 Conclusions

The current evidence suggests that cardiovascular diseases, cancers and type 2 Diabetes are important comorbidities of HIV infection. Policies and interventions targeting people living with HIV should prioritize the prevention of the risk of common Noncommunicable diseases along with the rapid scale up of HIV treatment. Integrated provision of HIV and NCD services for PLHIV could maximize synergy and improve efficiency.

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