Spatio-temporal description of AIDS-related cancers incidence in north and sub-Saharan Africa and of mortality in HIV-infected patients in Algeria and hepatitis C prevalence in patients with non-Hodgkin lymphoma in Algeria

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Spatio-temporal description of AIDS-related cancers incidence in north and sub-Saharan Africa and of mortality in HIV-infected patients in Algeria and hepatitis C prevalence in patients with non-Hodgkin lymphoma in Algeria

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To my family…

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Abstract and keywords

Abstract

Background: In Africa, the prevalence of HIV/AIDS and hepatitis C virus (HCV) has been the highest in the world. Furthermore, cancer incidence is increasing.

Objective: This thesis work presents a part of the impact of these infections on the cancer burden in northern and sub-Saharan Africa. AIDS-related cancers, namely Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer, were described to assess the impact of HIV/AIDS on cancer epidemiology in Algerian, Tunisian, Egyptian, Ugandan, and Zimbabwean populations. Furthermore, for the impact of HCV infection, the epidemiology of NHL as an extra-hepatic HCV-related cancer was also studied.

Results: Ugandan HIV/AIDS prevalence has declined since the early 1990s, and in Zimbabwe, after an increase until the end of the 1990s, rates have gone down. In Algeria, the retrospective study performed during this thesis work showed that risk of death and standardized mortality ratio, comparing the mortality of HIV-positive patients with that of the general population, have decreased after the introduction of highly active antiretroviral therapy (HAART) in 1998 in Algeria. However, the late stage of the disease among HIV/AIDS patients at diagnosis warns of the high risk of HIV/AIDS transmission. These observations suggest that Algeria needs to couple HAART use with a more effective prevention programme to fight the increase in the number of HIV/AIDS cases.
KS incidence was higher in the sub-Saharan African populations studied than in the northern African populations; however, among women it was similar in Uganda and Zimbabwe. With the emergence of the HIV/AIDS epidemic, KS incidence increased dramatically in both sub-Saharan African populations studied, and it has followed the HIV/AIDS time trend in Zimbabwe. However, in Uganda although HIV/AIDS prevalence has decreased, KS incidence has remained stable among women and elderly men (>50 years old). The decrease in KS incidence was observed only in young Ugandan men (<50

years old). In Uganda and Zimbabwe, we observed an equal or higher KS incidence in men than in women, whereas HIV/AIDS prevalence was higher among women.
In northern Africa, KS incidence has remained low and was similar between the populations studied. Regarding NHL, incidence has been highest among both genders in Egypt, while HIV/AIDS has been rare. In Egypt, NHL has seemed to be attributable to HCV infection. In Algeria, another country with low HIV/AIDS prevalence where NHL incidence has increased, a background investigation of NHL patients showed an HCV prevalence of 5.6%. HCV infection may partly explain NHL emergence, especially among a high-risk group of patients for HCV nosocomial contamination. In eastern Algeria, patients found with NHL and HCV infection were elderly women with primarily nosocomial risk factors for HCV contamination.
Cervical cancer followed the north–south HIV/AIDS distribution; however, its incidence varied among northern African populations where HIV/AIDS prevalence was similar.

Conclusion: KS, NHL, and cervical cancer epidemiology are related to that of HIV/AIDS; however, other infections – human herpesvirus 8 for KS, HCV for NHL, and human papillomavirus for cervical cancer – have influenced the geographical patterns and the time trends of these cancers.

Keywords

Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer, human immunodeficiency virus, acquired immunodeficiency syndrome, hepatitis C, Africa, Algeria, Egypt, Tunisia, Uganda, Zimbabwe, geographical patterns, time trends, case reports.

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List of abbreviations

AAPC: average annual percentage change

ABC: abacavir

AIDS: acquired immunodeficiency syndrome

ALAT: alanine transaminase

ALT: adult T-cell leukaemia/lymphoma

ANC: antenatal clinics

APC: annual percentage change

ART: antiretroviral therapy

ASAT: Aspartate transaminase

ASR: Age-standardized incidence rate

AZT: Zidovudine

CDC: Centers for Disease Control and Prevention

CHU : Centre hopitalo-universitaire (University Hospital Centres)

CIN: Cervical intraepithelial neoplasia

CI: Confidence interval

CT-scan: Computed tomography - scan

DNA: deoxyribonucleic acid

EBV: Epstein–Barr virus

EMC: Essential mixed cryoglobulinemia

ENT Consultation: Ear, Nose and Throat consultation

GPCR: The Gharbiah Population-Based Cancer Registry

HAART: highly active antiretroviral therapy

Hb: Haemoglobin

HBV: hepatitis B Virus

HCC: hepatocellular carcinoma

HCV: hepatitis C Virus

HHV-8: human herpesvirus 8

HIV: human immunodeficiency virus

HTLV-1: human T cell leukaemia/lymphoma virus type 1

ICD10: International Classification of Diseases, 10th version

ICD-O-3: International Classification of Diseases for Oncology, 3rd Edition

KS: Kaposi sarcoma

LDH: lactate dehydrogenase

MCH: Mpilo Central Hospital

NHL: non-Hodgkin lymphoma

ONS: Office of National Statistics

PCR: polymerase chain reaction

PEL: primary effusion lymphoma

R-CHOP: cyclophosphamide, hydroxydaunorubicin, Oncovin (or vincristine), and prednisone (or prednisolone)

RNA: ribonucleic acid

SIL: squamous intraepithelial lesion

SMR: standardized mortality ratio

SSA: sub-Saharan Africa

STD: sexually transmitted disease

STI: sexually transmitted infection

TCC: Tanta Cancer Center

UNAIDS: Joint United Nations Programme on HIV/AIDS

WHO: World Health Organization

3TC: lamivudine

1 Introduction

1.1 Human immunodeficiency virus

1.1.1 Virus

Human immunodeficiency virus type 1 (HIV-1) was discovered in 1983 and was firmly associated with acquired immunodeficiency syndrome (AIDS) in 1984 (Gallo et al., 1984). Later, a second virus (HIV-2) was discovered in West Africa. HIV-1 and HIV-2 are the only known human lentiviruses.

1.1.2 Epidemiology

At the end of 2010, an estimated 34 million people were living with HIV worldwide, an increase of 17% from 2001. This reflects the continued large number of new HIV infections and a significant expansion of access to antiretroviral therapy, which has helped reduce AIDS-related deaths, especially in recent years. The proportion of women living with HIV has remained stable at 50% globally, although women are more affected in sub-Saharan Africa (59% of all people living with HIV) and the Caribbean (53%). There were 2.7 million new HIV infections in 2010, including an estimated 390,000 among children. This was 15% less than in 2001, and 21% below the number of new infections at the peak of the epidemic in 1997(UNAIDS/WHO, 2011).

Sub-Saharan Africa remains the region most heavily affected by HIV. In 2010, about 68% of all people living with HIV resided in sub-Saharan Africa, a region with only 12% of the global population. Sub-Saharan Africa also accounted for 70% of new HIV infections in 2010, although there was a notable decline in the regional rate of new infections since the peak of the epidemic in 1997. The epidemic continues to be most severe in southern Africa, and South Africa has more people living with HIV (an estimated 5.6 million) than any other country in the world. Almost half of the deaths from AIDS-related illnesses in 2010 occurred in southern Africa. AIDS has claimed at least 1 million lives annually in sub-Saharan Africa since 1998. Since 1998 however, AIDS-related deaths have steadily decreased, as free antiretroviral therapy has become more widely available in the region. The total number of new HIV infections in sub-Saharan Africa has dropped by >26%,

down to 1.9 million in 2010 from an estimated 2.6 million at the height of the epidemic in 1997. In 22 sub-Saharan countries, HIV incidence declined by >25% between 2001 and 2009. These countries include some of the world's largest HIV epidemics in Ethiopia, Nigeria, South Africa, Zambia, and Zimbabwe. The annual HIV incidence in South Africa, although still high, dropped by a third between 2001 and 2009, from 2.4% to 1.5%. Similarly, the epidemics in Botswana, Namibia, and Zambia appear to be declining. The epidemics in Lesotho, Mozambique, and Swaziland seem to be levelling off, albeit at unacceptably high prevalence rates (UNAIDS/WHO, 2011).

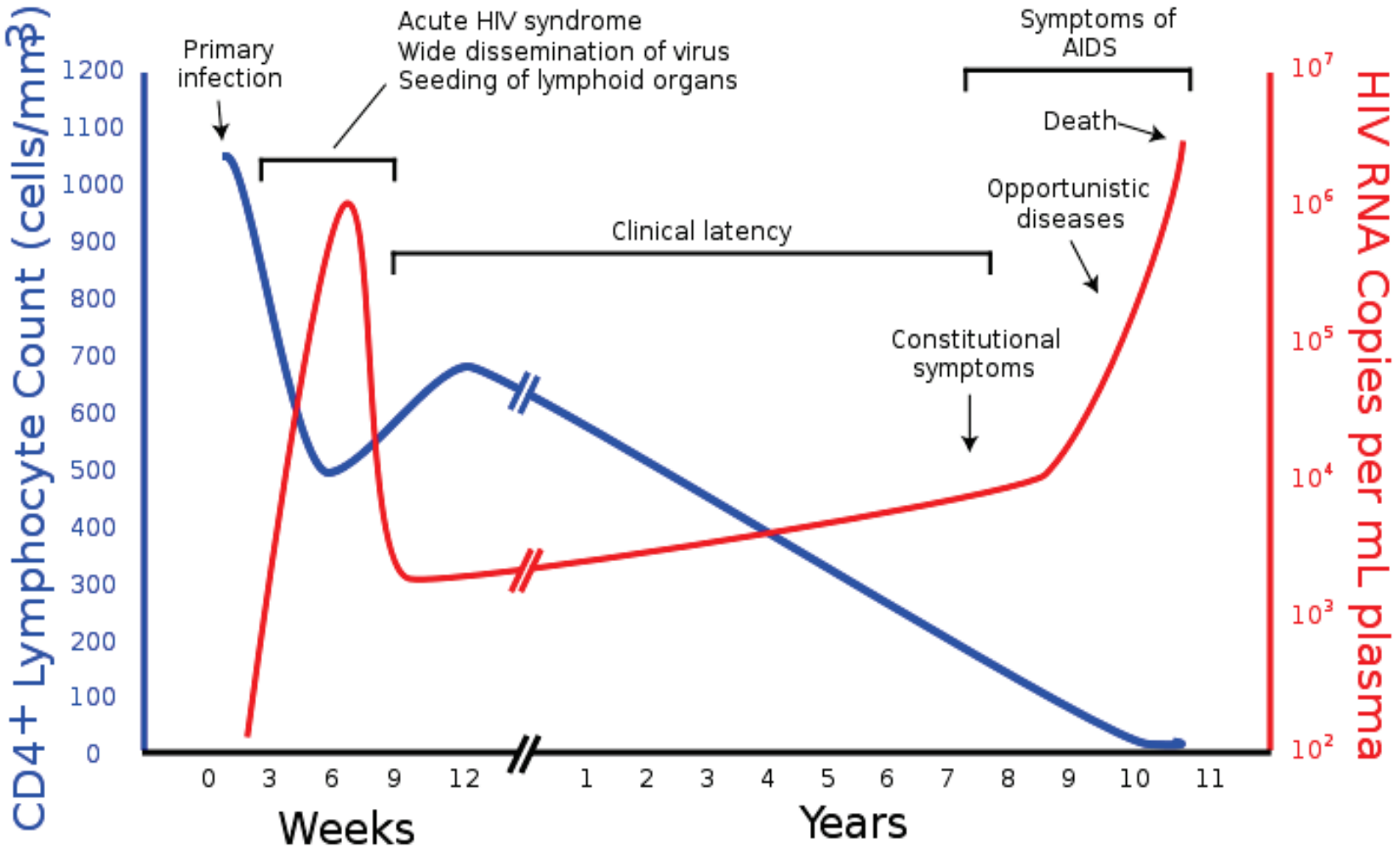
HIV-related trends in the Middle East and northern Africa vary; in some countries incidence, prevalence, and AIDS-related deaths are on the rise, whereas in others the epidemic is stable. Generally, HIV prevalence in the region is low, except in Djibouti and South Sudan, where the epidemic is becoming generalized (UNAIDS/WHO, 2011).

1.1.3 Natural history

HIV seroconversion syndrome refers to a complex of symptoms that occur in the first 1–6 weeks after HIV-1 infection in many adult patients (Tindall, 1988), during the period before HIV antibodies are detectable (Figures 1 and 2). After infection, there is a variable period during which most patients are asymptomatic but undergo progressive immunological decline. The incubation time between HIV infection and the appearance of clinical AIDS differs from one patient to another.

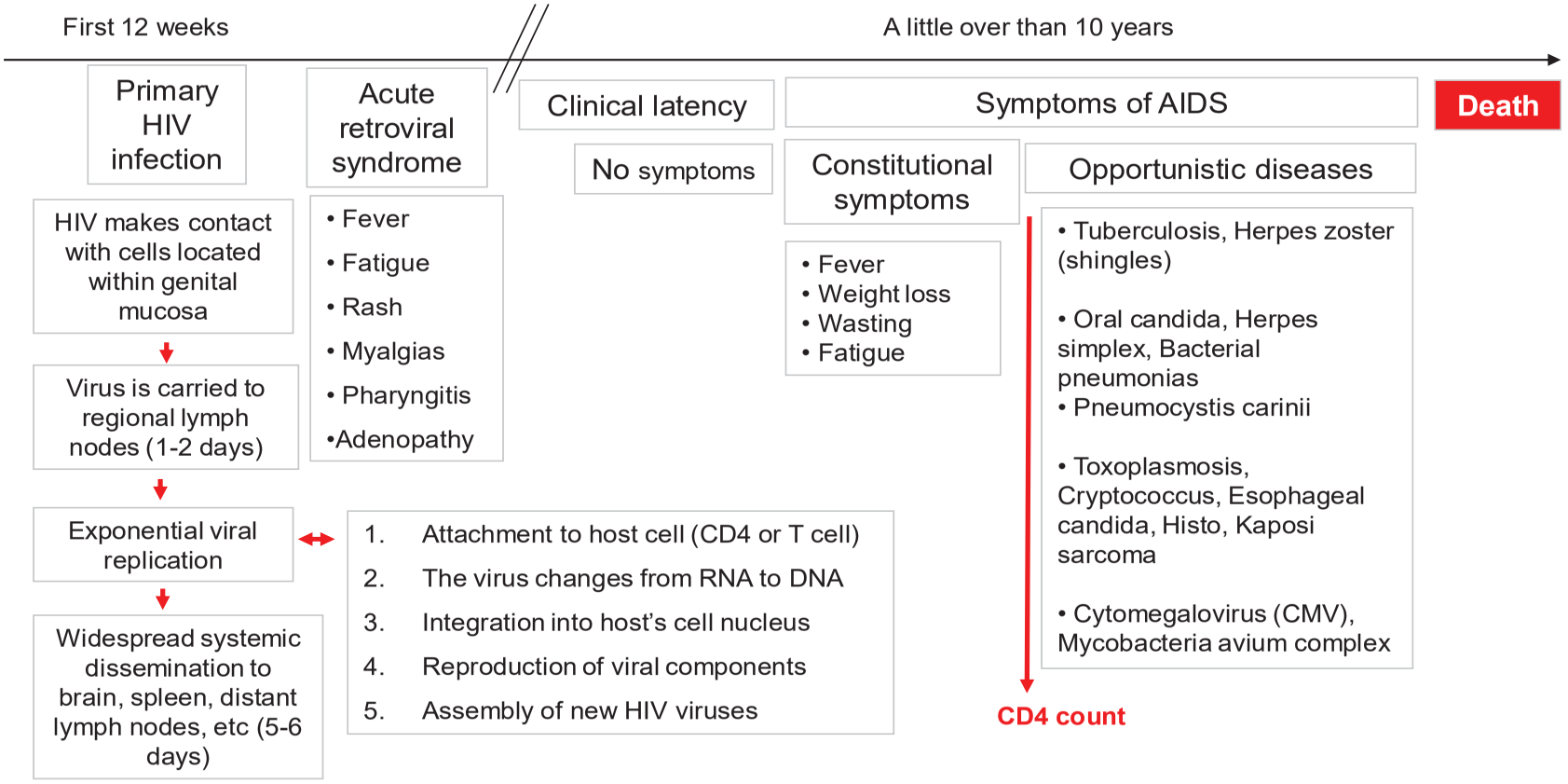
The use of the term "AIDS" has been complicated by changes in the definition and the need for different definitions according to the local situation. The first definition of AIDS was developed in 1982 by the US Centers for Disease Control and Prevention (CDC). Three cancers are included in the list of AIDS-defining conditions recognized by CDC: Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer. The other AIDS-defining conditions are almost all opportunistic infections (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1996b).

Figure 1: Relationship between HIV copies (viral load) and CD4 counts over the average course of untreated HIV infection



Adapted from (Fauci et al. 1996) .

Figure 2: Natural history of HIV infection



1.1.4 Transmission

The three primary routes of HIV transmission – sexual intercourse, blood contact, and from mother to child – were proposed on the basis of AIDS case reports (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1996b).

1.1.5 Prevention

In the absence of a vaccine, behaviour change remains necessary to stem the worldwide HIV epidemic. To prevent sexual transmission, two general categories of preventive activity are usually urged: reducing the number of sexual partners and modifying the type of sexual contact; and using condoms. Protection of sexual partners from exposure to semen, blood, and vaginal fluid during intercourse can be accomplished by the consistent and correct use of condoms. Behavioural intervention seems to have reduced the spread of HIV among intravenous drug users who share needles, syringes, and other blood-tainted effects (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1996b). Antibody-test screening of all blood or plasma donors has been universal in developed countries since the mid-1980s and has resulted in a marked reduction in HIV transmission by blood transfusion or use of clotting factor concentrates.

In Zimbabwe and Uganda, the decline of the HIV/AIDS epidemic has been attributed to increased access to antiretroviral therapy (ART) coupled with active prevention campaigns to increase public awareness (UNAIDS/WHO, 2011); (UNAIDS WHO, 2010); (Halperin et al., 2011). Highly active antiretroviral therapy (HAART), defined as a regimen of three or more antiretrovirals from two or more classes, represents the single most significant advance in the fight against HIV/AIDS. The vast majority of patients treated with HAART will experience long-term remission of HIV disease. Of course, HAART does not cure HIV infection but it changes the disease into a chronic and manageable condition. Use of HAART is associated with decreased HIV/AIDS-related morbidity, fewer opportunistic infections, and reduced mortality. Furthermore, evidence has also shown that HAART can reduce HIV transmission. This is most clearly illustrated in studies of vertical or mother-to-child HIV transmission.

Mother-to-child HIV transmission continues to threaten child survival worldwide. More than 2 million children are infected with HIV, the vast majority infected by mother-to-child

transmission in low- and middle-income countries (UNAIDS/WHO, 2011;World Health Organization, 2011). The persistence of mother-to-child HIV transmission underscores the importance of increasing access to strategies for effective prevention of mother-to-child transmission. The virtual elimination of mother-to-child HIV transmission has been achieved in most industrialized countries, with declines of >80–90% in the number of cases of perinatally acquired HIV infection, and mother-to-child transmission rates of <2–3% (Whitmore et al., 2012;Townsend et al., 2008;Tariq et al., 2011). The use of HAART, which is essential for elimination of mother-to-child transmission and contributes to maternal health, has been shown to be cost-effective compared with single-dose nevirapine in several low- and middle-income countries (Lorenzo et al., 2012); (Schmidt et al., 2012); (Robberstad and Evjen-Olsen, 2010); (Orlando et al., 2010).

Furthermore, research has shown that HAART use among HIV-discordant heterosexual couples in Africa was associated with a 92% reduction in HIV transmission. Until recently, the use of HAART among drug-using populations has remained controversial. However, HAART has now been shown to confer a similar survival benefit when individuals with and without a history of drug use were compared (Montaner et al., 2010).

1.2 Hepatitis C virus

1.2.1 Virus

Hepatitis C virus (HCV) is an RNA virus that belongs to the family of flaviviruses.

1.2.2 Epidemiology

The estimated prevalence of HCV infection worldwide is 2.2%. Region-specific estimates range from <1.0% in northern Europe to >3.0% in northern Africa (Alter, 2007). High prevalences of HCV infection (≥10%) were found in some areas of Italy and Japan and, most notably, in Egypt (15–20%) after mass injection treatment for schistosomiasis. The lowest HCV prevalence (0.01–0.1%) was reported for the United Kingdom and Scandinavia (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2011).

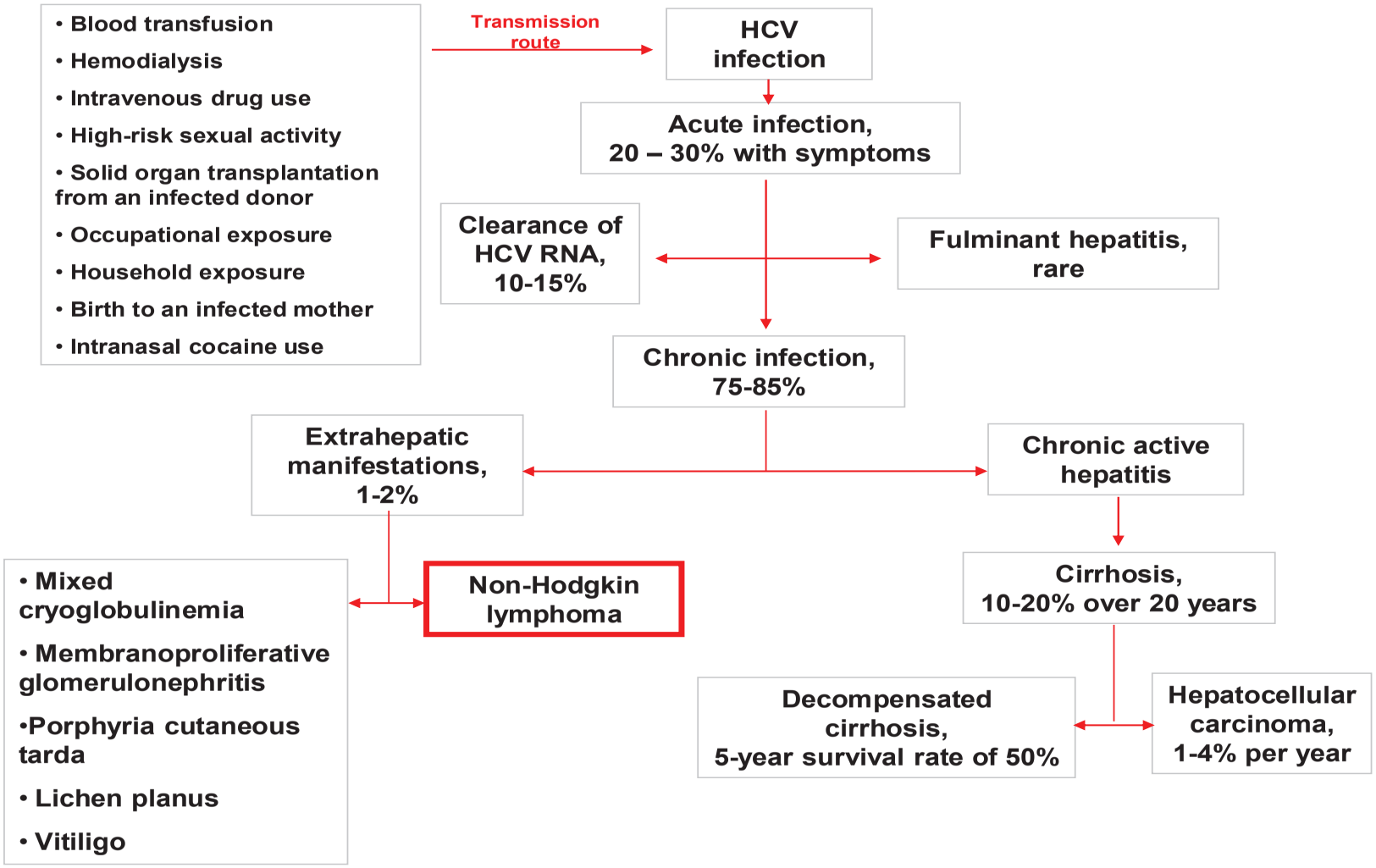
1.2.3 Transmission and prevention

HCV can be transmitted by transfusion of blood and blood products, transplantation of solid organs from infected donors, injection drug abuse, unsafe therapeutic injections, and occupational exposure to blood (primarily contaminated needles) (Alter, 2007). Iatrogenic HCV transmission through unsafe (therapeutic) injections has sustained substantial epidemics of the infection in Japan, Italy in the 1940s, and Egypt in the 1950s, and it occurs currently very frequently in low-income countries (Raza et al., 2007), where disposable needles tend to be re-used and injections tend to be preferred to the oral route for the administration of common treatments. It has been estimated that approximately 2 million HCV infections are caused annually by contaminated health-care-related injections. It is important to minimize infected blood exposure to avoid HCV transmission to healthy people. The rate of perinatal HCV transmission is 4–7%, and this occurs only when HCV RNA is detectable in the maternal serum at delivery. Furthermore, co-infection with HIV increases the rate of transmission 4–5-fold (Alter, 2007). To date, no active or passive vaccination against HCV is yet available (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2011).

1.2.4 Natural history

Persistence of HCV infection occurs in the majority of HCV-infected individuals. HCV infection is often asymptomatic. Indeed, acute HCV infection resolves spontaneously in only 10–15% of cases (Poynard et al., 2003); (Chen and Morgan, 2006) (Figure 3). Persistent HCV infection is characterized by the persistence of elevated aminotransferase levels and HCV RNA in serum. Serological distinction of chronic carriers is difficult. Chronically HCV-infected patients are in general asymptomatic, and some report non-specific symptoms such as fatigue or abdominal discomfort. Approximately 10–20% of chronically infected patients are estimated to develop cirrhosis. The time to progression to severe liver disease is highly variable. Factors that accelerate clinical progression include being of masculine gender, being older at the age of infection, alcohol intake, and co-infection with HIV and/or HBV (Lauer and Walker, 2001); (Chen and Morgan, 2006); (Alter, 2007).

Figure 3: Natural history of HCV infection



Adapted from Chen et al. 2006.

1.2.5 HCV-related diseases

HCV is hepatotropic and causes hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) (Lauer and Walker, 2001). An association between HCV seropositivity and HCC is observed, with relative risks ranging from 2.5 to 88 (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2011). HCV is also lymphotropic, and this infection is sometimes accompanied by autoimmune manifestations, most notably essential mixed cryoglobulinemia (EMC), which is characterized by cutaneous vasculitis, nephritis, peripheral neuropathy, and clonal B-cell lymphoproliferations (Gasparotto et al., 2002) (Cacoub et al., 1994). Other cancers than HCC, such as some non-Hodgkin lymphoma (NHL) subtypes (see Section 1.4.3.3), biliary tract/gallbladder cancer, leukaemia, and cancer of the thyroid, are also caused by HCV (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2011).

1.3 Kaposi sarcoma

In 1872, Kaposi described for the first time Kaposi sarcoma (KS) as a rare multifocal tumour involving blood and lymphatic vessels in elderly men of Jewish origin. Now, the tumour described by Kaposi is known as classic KS. Three other clinico-epidemiological forms have also been described (Sissolak and Mayaud, 2005). However, the histopathology is identical in all variants (Templeton, 1981); (Cockerell, 1991).

1.3.1 Four clinico-epidemiological forms

1.3.1.1 Classic KS

Classic KS is primarily a skin disease with a chronic indolent course that rarely metastasizes to other organs, and can sometimes regress. Patients survive 10–15 years before dying, often of unrelated causes. Most of th e cases seen in Europe and North America occur in elderly patients of Mediterranean or eastern European and Jewish origin, with a predominance of men (Safai et al., 1980).

1.3.1.2 Endemic KS

In the 1950s, as cancer registries became established in Africa, it was found that KS accounted for up to 8% of malignancies in some sub-Saharan regions, with an unusual endemic focus in parts of central Africa (Cook-Mozaffari et al., 1998). “African KS” has four different clinical variants: (i) a benign disease with few skin lesions, reminiscent of classic KS, but affecting instead young adults; (ii) an aggressive form mainly localized to extremities, with fungating and exophytic growth invading and destroying the subcutaneous and surrounding tissues, including the underlying bones; (iii) a lymphadenopathic form predominantly seen in prepubescent children, with minimal mucocutaneous lesions; and (iv) a widely disseminated disease with visceral involvement and near 100% fatality within 3 years (Taylor et al., 1971).

1.3.1.3 Iatrogenic KS

KS had also been observed in immunosuppressed patients after solid organ (renal) transplantation or after prolonged exposure to immunosuppressive therapy (Penn, 1979), at an average of 16.5 months after transplantation (Shepherd et al., 1997). In the 1960s

and 1970s, KS constituted up to 5% of cancers among immunosuppressed patients who had undergone organ transplantation (Penn, 1983;Penn, 1987;Penn, 1988). The course of the disease may be chronic or progressive, and spontaneous remission after discontinuation of immunosuppressive therapy is observed in the majority of patients (Brooks, 1986).

1.3.1.4 Epidemic KS

In the early 1980s, a fourth variant of KS heralded the onset of the AIDS epidemic in the United States (Hymes et al., 1981). In fact, it was initially described as a fulminant and disseminated form of Kaposi sarcoma, which occurred from 1981 in a cluster of cases among young homosexual or bisexual men in the United States without any recognized risk factor, and was later found to be associated with the newly recognized immunosuppressive syndrome, AIDS (Sissolak and Mayaud, 2005). Lesions are usually multiple, progress rapidly, and may affect any area of the skin as that of internal organs. The tumours frequently begin as dusky red or violet macules, progressing over weeks or months to raised, painless, firm nodules and plaques. Although the tumour may affect the legs, as seen with classic KS, lesions on the trunk, arms, genitalia, and face are also common (Smith and Spittle, 1987). Lymph nodes and the oral cavity, most notably the palate, may be extensively involved. Oral KS is often associated with involvement elsewhere in the gastrointestinal tract (Levine, 1993); (Regezi et al., 1993). Pulmonary KS generally presents with shortness of breath and cough, and it is clinically difficult to distinguish from other pulmonary complications of AIDS (Levine, 1993).

1.3.2 Etiological agent: Human herpesvirus 8

1.3.2.1 Viral life cycle

Humans are the natural hosts for human herpesvirus 8 (HHV-8). HHV-8, like all herpesviruses, can establish a lifelong latent infection in its human host. Latently infected cells provide a perpetual reservoir from which progeny viruses can be amplified for dissemination within the host and transmission between hosts. Peripheral blood CD19-positive B cells have been identified as a long-term latency reservoir for HHV-8; other cells, such as endothelial cells, may also be a site for HHV-8 latency, but they do not

appear to provide a long-term latent reservoir for the virus. Nonetheless, infected dermal endothelial spindle cells may release progeny virus that can subsequently infect local keratinocytes and the eccrine epithelium in the tumour. Lytic reactivation from latently HHV-8-infected cells that results in the release of progeny virions is a critical pathogenic step in multiple human diseases. In immunocompetent HHV-8 carriers, the immune system plays an essential role in tempering lytic reactivation of the virus (Lukac and Yuan, 2007).

1.3.2.2 Epidemiology of HHV-8

First identified as the cause of KS and termed HHV-8, HHV-8 is endemic in the Mediterranean basin with a prevalence that corresponds to the prevalence of KS before the AIDS epidemic. It is also endemic in sub-Saharan Africa but is uncommon in other regions of the world (Ascoli et al., 2002); (Schulz, 2000). Epidemiological studies indicate that HHV-8 is more prevalent in sub-Saharan Africa, several countries of southern Europe, the north African Mediterranean coast, and several countries of South America compared with northern Europe, North America, and Asia (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2011). Furthermore, although HHV-8 seroprevalence is low in the general US population, its prevalence among homosexual men in the United States ranges from 20% to 40% (Schulz, 2000).

1.3.3 Cofactor: Human immunodeficiency virus

The incidence of KS increased dramatically with the onset of the HIV epidemic. KS is an AIDS-defining condition (CDC staff members, 1993). It may occur at milder levels of immunosuppression than other AIDS-defining illnesses (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1996). HIV infection was found in 11/18 KS patients and in 8/200 control persons with other cancers in Rwanda (relative risk, 35.0) (Newton et al., 1995). The first record-linkage study performed in Africa showed a 6-fold increased risk of KS among people infected with HIV compared with the general population (Mbulaiteye et al., 2006).

1.4 Non-Hodgkin lymphoma

1.4.1 Classification

The World Health Organization (WHO) classification of lymphoid neoplasms has become the international standard (Fritz et al., 2000). The nomenclature for each distinctive disease entity reflects the postulated cell lineage and stage of differentiation. The cancer site (topography) definition of NHL is based on the International Classification of Diseases for Oncology 10 (ICD-10) (Fritz et al., 2000;Percy et al., 2010), as follows: C82–85, C96. The WHO classification combines morphological, immunophenotypic, genetic, and clinical features to group lymphomas into three major categories: B-cell neoplasm, T- and NK-cell neoplasms, and Hodgkin lymphoma. The Table 1 present B-, T- and NK-cell neoplasms.

Table 1: World Health Organization classification of lymphoid neoplasms

B-cell neoplasm	**T-cell and NK-cell neoplasm**
Precursor B-cell neoplasm	**Precursor T-cell neoplasm**
Precursor B-lymphoblastic leukaemia/lymphoma	Precursor T-lymphoblastic leukaemia/lymphoma
	Blastic NK-cell lymphoma
Mature (peripheral) B-cell neoplasms	**Mature T-cell and NK-cell neoplasms**
Chronic lymphocytic leukaemia	T-cell prolymphocytic leukaemia
Small lymphocytic lymphoma	T-cell large granular lymphocytic leukaemia
B-cell prolymphocytic leukaemia	Aggressive NK-cell leukaemia
Lymphoplasmacytic lymphoma	Adult T-cell leukaemia/lymphoma
Splenic marginal zone lymphoma	Extranodal NK/T-cell lymphoma, nasal type
Hairy cell leukimia	Enteropathy-type T-cell lymphoma
Solitary plasmacytoma of bone	Hepatosplenic T-cell lymphoma
Extraosseous plasmacytoma	Subcutaneous panniculitis-like T-cell lymphoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Mycosis fungoides
	Sezary syndrome
Nodal marginal zone B-cell lymphoma	Primary cutaneous anaplastic large cell lymphoma
Follicular lymphoma	Peripheral T-cell lymphoma, unspecified
Mantle cell lymphoma	Angioimmunoblastic T-cell lymphoma
Diffuse large B-cell lymphoma	Anaplastic large cell lymphoma
Mediastinal (thymic) large B-cell lymphoma	**T-cell proliferation of uncertain malignant potential**
Intravascular large B-cell lymphoma	Lymphomatoid papulosis
Primary effusion lymphoma	
Burkitt lymphoma/leukimia	
B-cell proliferations of uncertain malignant potential	
Lymphomatoid granulomatosis	
Post-transplant lymphoproliferative disorder polymorphic	

1.4.2 Epidemiology of non-Hodgkin lymphoma

NHLs were estimated are expected to account for 5.2% of cancer diagnoses and 5.7% of cancer deaths in Africa in 2008. With 37,282 cases diagnosed in adult men and women in

Africa in 2008, this group of malignancies is the sixth most incident Cancer in this continent (IARC, 2011). It is estimated that 55–75% of lymphomas worldwide present in the lymph nodes (Evans and Hancock, 2003).

1.4.3 Etiological agents

The number of viruses associated with lymphoma has increased over the past 30 years. These are retroviruses, herpesviruses, and HCV.

1.4.3.1 Retroviruses

Human T-cell lymphotropic virus type I (HTLV-I) was the first retrovirus established as a cause of lymphoma, specifically of adult T-cell leukaemia/lymphoma (ATL) (Cleghorn et al., 1995); (Gallo et al., 1981); (Manns et al., 1993). HTLV-I infection is endemic in southern Japan and in the Caribbean. It is also found in isolated parts of Africa, the Middle East, South America, Melanesia, and Papua New Guinea, but otherwise is rare, typically with seroprevalence <1.0%. HTLV-I can be transmitted from mother to child infant or by sexual activity, with easier transmission from men to women, but not through blood plasma.

Another retrovirus, HIV, is also associated with NHL (Beral et al., 1991). CDC (1982) included lymphoma of the brain as an AIDS-defining illness but subsequently expanded the case definition in 1985 and again in 1987 to include other specific NHL subtypes (Council of State and Territorial Epidemiologists, 1985 and 1987). NHL accounts for 3–5% of all initial AIDS diagnoses (Dal and Franceschi, 2003).

1.4.3.2 Herpesviruses

Among the herpesviruses, Epstein–Barr virus (EBV) infection is highly specific for Burkitt lymphoma, and HHV-8 infection for primary effusion lymphoma (PEL). EBV plays a role in other NHLs, including immunosuppression-related NHL, and extranodal NK/T-cell lymphoma (nasal type) (Bouvard et al., 2009). In 1995 HHV-8 was linked to a unique AIDS-related NHL (Cesarman et al., 1995), which subsequently was designated as PEL. HHV-8 is also associated with multicentric Castleman disease-plasmablastic lymphoma (Bouvard et al., 2009). These HHV-8-related NHL subtypes are associated almost

exclusively with HIV infection and appear to develop in the setting of profound immunosuppression, particularly PEL (Cesarman and Knowles, 1997).

1.4.3.3 Hepatitis C virus

The association between HCV and NHL has been newly identified (Bouvard et al., 2009), but the mechanism of pathogenesis remains unclear. Chronic infection with HCV was evaluated as “carcinogenic to humans” (Group 1) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2011). Studies have found an approximately 2-fold excess risk of either NHL generally or B-cell NHL among HIV-negative individuals infected with HCV (Ohsawa et al., 1999); (Duberg et al., 2005); (Ulcickas et al., 2007). Up to 13% of patients with B-cell NHL have HCV antibodies Furthermore, 10% of patients with cryoglobulinemia, the vast majority of whom have chronic HCV infection, developed NHL over a 10-year follow up period (Meyer and Bodenheimer, 2009).

1.4.4 Cofactor: Human immunodeficiency virus

Systemic AIDS-related NHLs are a heterogeneous group of malignancies, usually of the B-cell phenotype. Three B-cell NHLs (Burkitt lymphoma, immunoblastic lymphoma, and primary lymphoma of the central nervous system) are clinical conditions in the 1993 AIDS surveillance case definition (CDC staff members, 1993). NHL is considered to be a relatively late manifestation of AIDS compared with KS and some opportunistic infections. HIV is indirectly responsible, via immunosuppression, for the emergence of NHL (Bouvard et al., 2009). The first record-linkage study performed in Africa showed a 7-fold increased risk of NHL among people infected with HIV compared with the general population (Mbulaiteye et al., 2006).

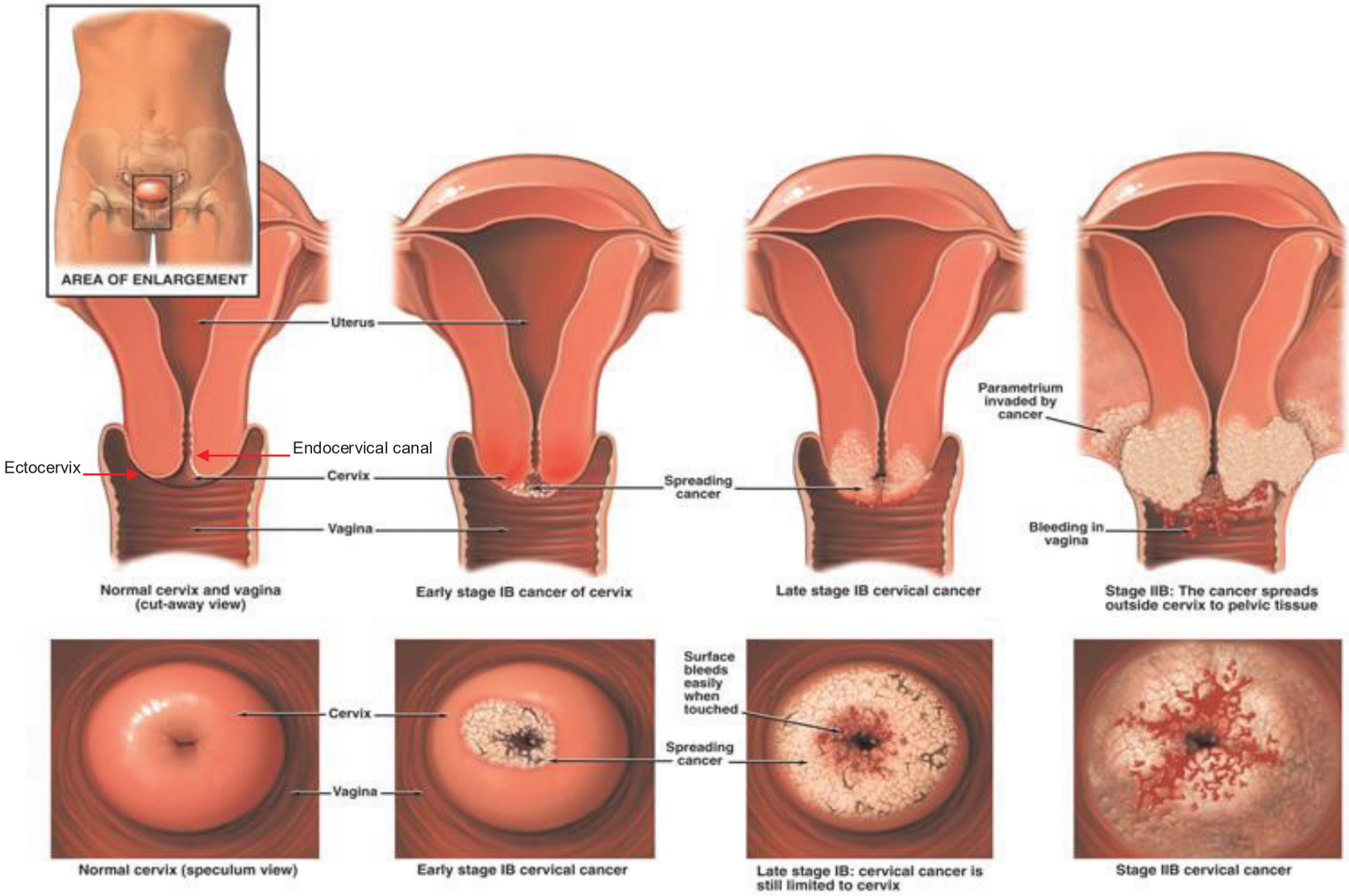
1.5 Cervical cancer

Cervical cancer is an important public health problem worldwide. It is the most common cancer among women in sub-Saharan Africa and ranks second in northern Africa, after breast cancer (IARC, 2011).

1.5.1 Anatomical distribution and cervical transformation zone

The cervix is the cylindrically shaped lower third of the uterus extending into the vagina from the anterior vaginal wall (Figure 4). The part of cervix that projects into the vagina, called the ectocervix or portio vaginalis, is covered by non-keratinized stratified squamous epithelium similar to the neighbouring lining of the vagina (Kurman, 2002). The endocervical canal is covered by tall, mucus-secreting columnar cells of the same embryological derivation as the uterine endometrium. At birth, the columnar epithelium extends out onto the ectocervix, but with age the position of the squamocolumnar junction recedes into the endocervical canal as columnar epithelium is replaced by squamous epithelium in a process called squamous metaplasia. The metaplastic area adjacent to the receding squamocolumnar junction is called the transformation zone, and this area has a unique sensitivity for neoplastic events (Jacobson et al., 1999). The reasons for the special susceptibility of the transformation zone are unknown.

Figure 4: Cervical cancer and precancerous stages

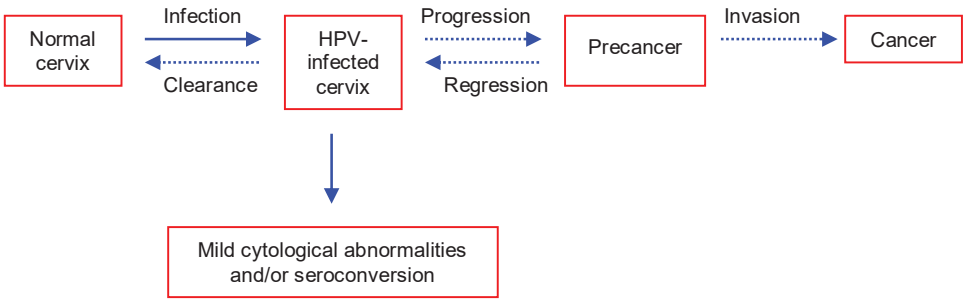


Adapted from: http://www.stage4cancers.info.

1.5.2 Three stages of cervical carcinogenesis

Cervical carcinogenesis is a multistep process. There are three major, necessary stages in cervical carcinogenesis (Figure 5): human papillomavirus (HPV) infection, progression of infection to precancer, and invasion. Backward steps can occur also, namely clearance of HPV infection and, less frequently, regression of precancer to normalcy.

Figure 5: Model of multistage cervical carcinogenesis



1.5.2.1 Infection with the etiological agent: Human papillomaviruses

Risk factors for cervical cancer include classic demographic variables (e.g. social status, religion, occupation, marital status, and ethnicity), sexual and reproductive variables, male circumcision, smoking, alcohol intake, use of oral contraceptives, genital hygiene, and infections (HPV and HIV). The sine qua non of cervical cancer and precancer is the presence of transcriptionally active oncogenic HPV DNA. The main types of HPV found as etiological agents of cervical cancer are HPV-16, 18, 31, 33, 35, 45, 52, and 58 and four types less constantly found, HPV-39, 51, 56, and 59. All these types were classified as “carcinogenic to humans” (Group 1). The risk of cervical cancer may be an order of magnitude higher for HPV-16 infection than for other high-risk HPV types. HPV-68 was classified as “probably carcinogenic to humans” (Group 2A), on the basis of limited evidence in humans and strong mechanistic evidence. The other types of HPV in the high-risk alpha species were classified as “possibly carcinogenic to humans” (Group 2B). Finally, HPV-6 and HPV-11 were evaluated as “not classifiable as to their carcinogenicity to humans” (Group 3) on the basis of inadequate epidemiological evidence and absence of carcinogenic potential in mechanistic studies (Bouvard et al., 2009).

1.5.2.2 Cervical precancer

Infection with an oncogenic HPV type, with or without macroscopic and microscopic signs, is extremely common and is usually benign. Cervical precancer (cervical intraepithelial neoplasia, CIN) is relatively rare by comparison, and represents a truly pre-malignant lesion in the most severe cases (carcinoma in situ). Furthermore, it is a non-trivial task to define “precancer” because there is still heterogeneity in the microscopic diagnoses. Some precancers represent acute HPV infections of particularly bad microscopic appearance that are destined to regress. Others are incipient precancer destined to persist with high risk of invasion. Infections with non-oncogenic HPV types are capable of producing lesions diagnosed as precancer, showing that this level of abnormality is not a perfect surrogate for cancer risk (Clifford et al., 2003). Better accuracy of diagnosis based on molecular profiling is the goal.

1.5.2.3 Cervical cancer

In early infection and precancer, HPV is typically found as circular double-stranded DNA. However, invasive cancers often (but not always) contain linear HPV DNA that has integrated into the host genome (Wang and Hildesheim, 2003).

Approximately 80% of invasive cervical cancers are squamous cell carcinomas of epithelial origin (Wang et al., 2004). The remaining 20% of tumours consist largely of adenocarcinomas, with mixed adenosquamous cell carcinomas and other rare histological type.

1.5.3 HIV and cervical cancer

In 1993, CDC expanded the AIDS surveillance case definition to include invasive cervical cancer as a further AIDS-defining clinical condition (CDC staff members, 1993). However, none of the case–control studies of HIV and cancer conducted in Africa have shown an excess risk of cervical cancer among HIV infected women. There is, however, evidence that the risk of pre-invasive disease (CIN) is increased in the presence of HIV infection (Parkin et al., 2003).

1.5.4 Prevention

Control of cervical cancer has traditionally been through programmes of detection by cytology and treatment of precursor lesions (dysplasia/carcinoma in situ, CIN, squamous intraepithelial lesion). Organized screening programmes in many European countries have been successful in reducing incidence and mortality rates from levels that, before these programmes were introduced, were not so different from those seen today in much of Africa. That the traditional Pap smear can give significant protection against development of invasive cancer has been demonstrated in many case–control studies (Parkin, 1997), including one in Morocco (Chaouki et al., 1998).

However, screening programmes in Africa have been very limited in scope, and all have been centred on hospitals or family planning clinics, rather than being population-based. Reports have been published on limited screening projects in various countries (Parkin et al., 2003). However, population coverage remains very low. A survey of cytology laboratories in four countries (Côte d'Ivoire, Guinea, Mali, and Senegal), in about 1995, estimated that <1% of women aged ≥15 years had undergone a smear test that year (Woto-Gaye et al., 1996).

The difficulties in implementing community screening programmes in developing countries using the Pap smear have become increasingly obvious in recent years. The reasons lie in the logistics of organization for all phases of the programme (screening, diagnosis, and follow up) and in the problems of maintaining good-quality cytology laboratories. For this reason, there has been increasing interest in alternative screening strategies that may be easier to apply. In particular, much attention has focused on the value of screening by visual inspection after acetic acid impregnation of the cervix (Sankaranarayanan and Pisani, 1997).

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2 Aim of the thesis

In this thesis, I describe HIV and HCV infection rates and the incidence of cancers related to these infections in regions across Africa.

The aims of the thesis are:

- To describe the geographical patterns of the three most common AIDS-related cancers in Africa;
- To give an overview of the time trends of HIV/AIDS and KS in two sub-Saharan African populations, namely Uganda and Zimbabwe;
- To present the changes in the number of newly HIV/AIDS diagnosed cases over 23 years in north eastern Algeria and to investigate the cancer emergence among these HIV/AIDS patients;
- To quantify the changes in mortality trends among HIV positive patients before and after the introduction of highly active antiretroviral therapy in north eastern Algeria;
- To describe the prevalence of HCV among patients with NHL in eastern Algeria; and to see whether HCV infection could be one of the risk factors for NHL, as observed in Egypt.

The epidemiology of HIV and HCV infections in Algeria was described by means of a study designed and carried out during my thesis research work.

Section 4.1 focuses on the description of the geographical variations of KS, NHL, and cervical cancer in the period 1998–2002 using cancer registry data from Setif (Algeria), Sousse (Tunisia), Gharbiah (Egypt), Kyadondo (Uganda), and Harare (Zimbabwe).These populations are located in two African regions with the highest prevalence rates in the world: sub-Saharan Africa for HIV infection, and northern Africa for HCV infection.

Trends in age-standardized incidence of KS in the general populations of Harare (Zimbabwe) and Kyadondo (Uganda) since the 1960s are presented in **Section 4.2**. This section presents how KS incidence trends varied according to the HIV/AIDS epidemic changes (its emergence and its decline) in these two populations.

Whereas the HIV/AIDS epidemic has been declining and results of the decline in KS incidence trends in both these sub-Saharan populations presented above, HIV/AIDS rates are increasing in northern Africa.

Trends in HIV/AIDS mortality in north-eastern Algeria, comparisons with general population mortality, the impact of the introduction of HAART on HIV/AIDS rates, and the investigation of cancer emergence in HIV/AIDS patients are presented in **Section 4.3**. One HIV-infected patient with very late presentation at diagnosis is described in a case report (**Section 4.4**) as a picture of the Algerian concerning situation, where efforts should be made in early detection of HIV-positive patients.

Despite the introduction of HAART, which should increase patients' life expectancy and should allow the emergence of long-latency cancer, no AIDS-related NHL was observed in the Algerian patients studied. HCV is one of the main etiological agents of NHL in Egypt, where HIV/AIDS prevalence is low. The two cases of HCV diagnosed among the patients with NHL in north-eastern Algeria during the period 2009-2010, were described in **Section 4.5**. The prevalence of HCV among patients with NHL was higher than in general population. This result suggests HCV as one of the existing causes of NHL emergence in Algeria, where HIV/AIDS prevalence remains low.

The **General discussion Chapter** discusses the main results of the spatiotemporal analyses and the study presented in this thesis, as well as perspectives for current and future research, prevention of HIV/AIDS, and clinical management of infection-related cancer.

3 Methods

3.1 Population-based data sources

Data collected by population-based cancer registries around the world have been sent to IARC to be checked for data quality and to be used for international comparative studies and publications.

The cancer incidence data used in my research work were from six regional cancer registries in Africa: those of Setif (Algeria), Gharbiah (Egypt), Sousse (Tunisia), Kyadondo County (Uganda), and Harare and Bulawayo (both in Zimbabwe) (Figure 6). I have used grouped data by 5-year age group, sex, and by populations from these six registries to describe the geographical patterns of the three AIDS-related cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) in Setif, Gharbiah, Sousse, Kyadondo County, and Harare for the period 1998–2002, and to describe time trends in Kaposi sarcoma (KS) incidence in Zimbabwe (Harare and Bulawayo) and Uganda (Kyadondo County) since the 1960s. The national HIV/AIDS prevalence data by country were obtained from the Joint United Nations Programme on HIV/AIDS (UNAIDS and WHO, 2010) and used to compare HIV/AIDS geographical patterns and time trends with those of AIDS-related cancers.

The following subsections of section present HIV/AIDS data sources used by UNAIDS to estimate prevalence rates, and the six African cancer registries from which some of the data that I used for my thesis work were obtained.

Figure 6: Location of the six African population-based cancer registries studied (green dots)

3.1.1 Joint United Nation Programme on HIV/AIDS data sources

The precise numbers of people living with HIV, people who have been newly infected, and people who have died of AIDS are not known. Achieving 100% certainty about the numbers of people living with HIV globally, for example, would require testing every person in the world for HIV every year—which is logistically impossible and poses ethical problems. But it is possible to estimate those numbers by using other sources of data.

The UNAIDS/WHO estimates are based on all pertinent, available data—including surveys of pregnant women attending antenatal clinics (ANCs), population-based surveys (conducted at the household level), sentinel surveillance among populations at higher risk of HIV infection, case reporting, and other surveillance information. Different sets of data are used to calculate estimates of HIV prevalence for generalized (or high-level) epidemics—where HIV is firmly established in the general population and sexual networking is sufficient to sustain an epidemic independent of subpopulations at higher risk of infection—and concentrated (or low-level) epidemics—where HIV is concentrated in groups with behaviours that expose them to a high risk of HIV infection.

For countries with high-level or generalized epidemics (e.g. Zimbabwe, Uganda), estimates of HIV prevalence are primarily based on surveillance among pregnant women attending sentinel ANCs. Such data are collected on an annual basis and are currently primary basis used by UNAIDS for the assessment of trends. Population-based sample surveys that include testing for HIV infection (conducted much less frequently) are used to improve the estimates based on ANC data. If countries have conducted such a survey, the results are used to calibrate the trends in HIV prevalence. If countries have not conducted such surveys, the HIV prevalence trends are calibrated based on the “global default” adjustments derived from the comparison of HIV prevalence between national surveys and ANC surveillance in other countries.

For countries with low-level or concentrated epidemics (e.g. Algeria, Egypt, Tunisia), HIV estimated rates are based on studies among key populations who are at higher risk of HIV exposure—such as intravenous drug users,, sex workers, or men who have sex with men. Countries with concentrated epidemics sometimes have additional sources of data, which can help refine estimates. In countries with high coverage of voluntary counselling

and testing programmes, case reports can add to the estimation process and make estimates more precise.

Better data from country surveillance and steady improvements in the modelling methodology are enabling UNAIDS/WHO to develop more accurate estimates (UNAIDS/WHO, 2011).

3.1.2 Quality of HIV/AIDS data

The use of antenatal and household surveys in estimating HIV infection levels for generalized epidemics has strengths and weaknesses. Estimates based on ANC attendees generally provide a good indication of HIV infection trends over time among adults aged 15–49.

Studies have shown that high proportions of women in most of the highly affected countries have access to ANC services. Where possible, estimates derived from ANC data have been compared at the local level with HIV prevalence data acquired in community-based surveys. Such validation exercises have concluded that estimates based on ANC sentinel surveillance provide a good approximation of HIV prevalence among adults aged 15–49 (men and women combined) in the local community. However, ANC surveillance is limited in that it only samples pregnant women attending public health services and therefore excludes women who are not pregnant or sexually active and who do not attend public health clinics. The most important limitation is often related to the selection of sentinel ANCs. In general, clinics with larger volumes of pregnant women are included to obtain the minimum required sample size during the few weeks of the annual survey of sentinel ANCs. Such clinics are more likely to be in urban areas, and the sample of clinics is often not geographically representative. Remote rural clinics are underrepresented for the most part, although countries are increasingly trying to increase their representation as in-country surveillance efforts are expanding.

National population-based household surveys, however, can reveal important information about the national prevalence level and about the spread of HIV in a country. These surveys are generally geographically representative and can provide estimates for the general population as well as for different subgroups, such as prevalence in urban and rural areas, men and women, different age groups, and different regions. However,

population-based surveys by their nature exclude certain high-risk populations (e.g. people living in hostels, army recruits) and might therefore underestimate HIV prevalence. Non-response due to absence from households and refusal to participate in these surveys could also lead to bias in the HIV estimates. Current research, however, indicates that in most instances these biases are relatively small.

Population-based surveys are costly, complex undertakings, especially if biological testing is included. Therefore, they are conducted with long intervals between surveys, and few countries have conducted more than one national survey with HIV testing since 2000.

Considered together, the various data sources can yield more accurate estimates of HIV infection levels and the demographic impact of AIDS. However, HIV estimates (whether derived from household surveys or sentinel surveillance data) need to be assessed carefully, and the data and assumptions reviewed continually.

For all diseases, a sound population-based sample provides better estimates of disease prevalence than a clinic-based sample. National population-based surveys reveal important information about the national prevalence level and about the spread of HIV, particularly among young people, men, and residents in rural areas. If response rates are good (e.g. >75%) and there is no evidence of systematic biases of exclusion of a large proportion of the population with likely different levels of HIV infection, then national estimates that consider data from all sources (surveillance, population-based surveys, and mortality data, if available) should be a good estimation of the true situation be close to the true situation.

Case reporting generally tends to substantially underestimate the number of people living with HIV. Most countries that rely on case reporting focus the data collection on specific at-risk groups, often missing other groups. Often, case reporting tends to focus heavily on injecting drug users, and often the data collected reflect trends only among those users who interact with government authorities (e.g. by being arrested or attending drug treatment clinics).

However, in countries that have extensive voluntary counselling and testing programmes, case reports may enable more precise estimates to be developed. Nonetheless, case reporting is unlikely to capture people living with HIV who were recently infected and who

therefore present no symptoms of infection. For these reasons, case reports can only indicate the minimum number of people living with HIV.

In contrast, reliance on sentinel surveillance of at-risk groups can lead to overestimation of HIV prevalence in these groups. This is because such surveillance in some cases detects HIV infection rates among individuals who are at highest risk of HIV infection. For example, sentinel surveillance among sex workers or their clients often focuses on those who seek treatment at sexually transmitted infection (STI) clinics—and who, by definition, have had unprotected sex. However, other sex workers and clients who do practice safer sex—and who therefore tend not to present at these clinics with STIs—generally are not captured in this surveillance (UNAIDS/WHO, 2011).

3.1.3 Setif Cancer Registry (Algeria)

3.1.3.1 Registration area

The Setif Cancer Registry covers the population of 60 communes. The population at the 1998 census was 1 299 117, representing 4.33% of the overall Algerian population, which makes Setif the second largest population centre after Algiers. In 2001, the population growth rate for this area was 1.8%. About 48% of the population live in rural areas, and 99% are Sunni Muslims. The wilaya (administrative division) of Setif covers an area of 6504 km2, corresponding to 0.27% of the country. The wilaya of Setif is the capital of the highlands, with an altitude of 1300 m and a semi-arid continental climate.(Curado MP et al., 2008).

3.1.3.2 Cancer care facilities

General health care in the region is provided predominantly by the University Hospital Centre (CHU) and 6 other hospitals, 16 health centres, and 55 primary care centres. These are supplemented by private practitioners and hospitals for a total of 2115 beds, or 1 bed per 690 inhabitants. The total number of health workers is 4072: 215 public specialists, 198 private specialists, 387 public generalists, 278 private generalists, 2944 public nurses, and 50 private nurses. The CHU, located in Setif, provides cancer surgery and chemotherapy services. Radiotherapy is provided by the cancer centres of Constantine (120 km away) and Algiers (300 km away), and as a result many patients are

treated in Algiers and Constantine. All breast cancers are treated at the breast health centre in Algiers. A large new cancer centre is now being constructed implemented in Setif and is expected to provide care for all cancer patients from the area of about 5 million inhabitants in 2008 (Curado MP et al., 2008).

3.1.3.3 Registry structure and methods

The registry, founded in 1989, is located in the epidemiology and preventive medicine service of the Hôpital Mère-Enfant of the CHU of Setif under the auspices of the Ministry of Health and Ministry of Research and Education. The registry is staffed by two epidemiology assistants, one pathology assistant, one technician in epidemiology, and three postgraduate students in epidemiology. The Setif Cancer Registry uses active case finding from 16 sources of data consisting of CHUs University Hospital Centres, cancer hospitals, public health hospitals, pathology laboratories, private hospitals and offices, insurance offices, other cancer registries in Algeria, and death registration offices. The death registration system is incomplete; the death certificates are examined and a record completed for each certificate mentioning cancer or malignant tumour. Collection is primarily active. For each patient, data are collected from four or five different sources, which permits the information to be completed and checked before coding. For each cancer case, a limited number of variables (18) have been put into a sample record. The variables include the sources of information. For the tumour, only four variables are collected, including the date of diagnosis, the site, and the morphology. The data are coded according to ICD-O. Impossible or improbable combinations (site, sex, age, and morphology) are identified by computer. Duplicate registrations have been reduced to a minimum thanks to a careful control of name, sex, date of birth, and diagnosis. The registry staff visit these sources of data once a month (Curado MP et al., 2008).

3.1.4 Gharbiah Population-Based Cancer Registry (Egypt)

3.1.4.1 Registration area

The Gharbiah Population-Based Cancer Registry (GPCR) covers eight districts (Tanta, Elmahalla Elkobra, Kafr Elzayat, Zefta, Kotour, Elsanta, Basyoun, and Samannoud) within the state of Gharbiah, in the west and central delta region in lower Egypt. The population

at the most recent census (1996) was 3.406 million (5.7% of the total population of Egypt). About 40% of the population lives in urban areas. The majority are Muslims, and the remainder are Christians (Curado MP et al., 2008).

3.1.4.2 Cancer care facilities

General health care in the region is provided predominantly by the Gharbiah Health Services Department (Ministry of Health and Population), through the district hospitals and a network of primary health centres. These are supplemented by Tanta University Hospital, insurance hospitals and clinics, private practitioners, and private hospitals. The Tanta Cancer Center (TCC) is located in Tanta, the principal town and capital of Gharbiah, and provides cancer surgery and chemotherapy services. Gharbiah Cancer Society, nongovernmental organisation and the radiotherapy department at Tanta University Hospital in the vicinity of TCC provide radiotherapy services. In the registry area, patients at the primary and secondary care facilities suspected to have cancer are generally referred to TCC or to one of the two hospitals with comprehensive cancer services within a 60 km radius (Mansoura Urology Center and Mansoura Gastroenterology Center) or to the National Liver Institute, Menoufeya University (40 km away), or occasionally to the National Cancer Institute, Cairo University (100 km away) (Curado MP et al., 2008).

3.1.4.3 Registry structure and methods

The registry is located within TCC and is sponsored by the Middle East Cancer Consorsium,; the U.S. National Cancer Institute, Bethesda, USA; and the Ministry of Health and Population, Cairo, Egypt. A principal investigator, an executive director, two co-investigators and field supervisors, two data managers, four part-time registrars, and four full-time secretaries staff the registry. GPCR uses active case finding from 57 sources of data, consisting of cancer hospitals, general hospitals, university hospitals, insurance hospitals, private hospitals and clinics, specialized hospitals and centres, pathology and haematology laboratories, and the district death registration offices.

The death registration system is adequate; the cause of death from cancer is often mentioned. The registry staff visits these sources, where they scrutinise the records kept in medical records departments and the registers of individual departments concerned

with diagnosis and treatment of cancers in order to identify and abstract information on cases of cancer, diagnosed by all methods, among residents of the registry region. Although cancer is a notifiable disease by administrative order (without a specific law), few registration forms are received from private practitioners. Arrangements have been made with the hospitals outside the registration area to be visited every 1–3 months, according to workload, in order to abstract resident cancer cases that are diagnosed and treated in those hospitals (Curado MP et al., 2008).

3.1.5 Central Region Cancer Registry, Sousse (Tunisia)

3.1.5.1 Registration area

Tunisia, an Arab-Islamic country in northern Africa, is usually divided into three regions: the northern, central, and southern regions. The Central Region Cancer Registry includes six provinces: Sousse, Monastir, Mahdia, Kairouan, Kasserine, and Sidi Bouzid. Sousse province, which has an area of 2669 km2 and contains the capital city of the central region, had a population of 495 000 in 2000, 18.3% of the overall population of the central region (2 697 200). The population is relatively young; 48.1% are <20 years old, and 8% are >60 years old. The main economic sectors of the region are agriculture, industry (textiles), and tourism (Curado MP et al., 2008).

3.1.5.2 Registry structure and methods

The Central Region Cancer Registry, staffed by four full-time physicians, is located in the Department of Pathology of the University Hospital of Sousse. The search for new cases is proactive, which means that the registry does not wait to be informed but actively looks for information from certain specific sources. Primary sources include the Departments of Pathology of the public and private medical centres (five, three of which are in Sousse). The other primary sources are the Departments of Radiotherapy (in Sousse), Oncology (in Sousse), and Haematology, in addition to the other 24 departments of the University Hospital of Sousse. In addition to the histologically confirmed cases, more and more cases have been discovered in recent years without microscopic confirmation and are related to the gall bladder, pancreas, prostate, lungs, and ovaries (Curado MP et al., 2008).

3.1.6 Cancer registries of Harare and Bulawayo (Zimbabwe)

3.1.6.1 Registration area

Harare is located in north-eastern Zimbabwe and is the capital city. The population of the city according to the 2002 national census was 1.9 million (Curado MP et al., 2008). Bulawayo, the second largest city in the country, is located in south-western Zimbabwe, and its population according to the 2009 national census was 1.5 million (Skinner et al., 1993). The national population was 11.6 million in 2002 (Curado MP et al., 2008).

3.1.6.2 Cancer care facilities

The current difficult economic situation in Zimbabwe is negatively affecting health care delivery, particularly in the public sector. In spite of this, the system in Zimbabwe, based on a network of primary health care facilities provided by the municipality, government-funded referral facilities, and a private sector that caters mainly to middle- and higher-income groups, continues to perform reasonably (Curado MP et al., 2008).

3.1.6.3 Harare registry structure and methods

The Zimbabwe National Cancer Registry was established in 1985 in Harare as a result of an agreement between IARC and the Zimbabwean Ministry of Health. The target population of the registry is that of Harare city, and adequate population coverage was achieved in 1990. Although the registry records all cancer patients identified from its diverse sources irrespective of residence, the analysed data for 1998–2002 are confined to the Harare city population. The activities of the registry are overseen by a constituted advisory committee, and the day-to-day administration is the responsibility of the registrar under the guidance of the medical director. The registry has four full-time staff, comprising the registrar, a secretary, and two data collection clerks. It is strategically located at Parirenyatwa Hospital, a large government referral centre and also the location of the University of Zimbabwe College of Health Sciences. The registry is supported by the Ministry of Health and Child Welfare, IARC, and other organizations. Case finding is mainly active; the registry staff visit institutions within the health care delivery system that are involved in the management of cancer patients. The registry information sources include:

• Routine weekly visits to the inpatient wards of the two government central referral hospitals (Harare and Parirenyatwa);

• Medical records of discharged and deceased cancer patients from the two central hospitals, and visits to oncology outpatient clinics;

• Histology reports from the public and private sectors, medical records of the radiotherapy department, death certificates of patients dying of cancer in greater Harare, and records of specific clinical research studies.

Hospital inpatients are interviewed to verify the accuracy of reported age, residential status, and other demographic data. Information recorded on each case includes sex, date of birth or age, residence, racial group, basis of diagnosis, tumour site, and histology. Residence status is defined as the patient's place of residence during the previous six months. All notifications coming into the registry are thoroughly vetted to ensure that only incident cases are recorded. Incident cases are verified by the treating doctors to confirm the diagnosis, and completed forms are coded. The data are stored electronically using the IARC/IACR CanReg system. Patient name lists are generated periodically to physically eliminate duplicates. When several lesions of the same histological type occur in a patient, only the first lesion is recorded. Subsequent lesions are ignored. For example, the incidence of non-melanoma skin cancer is very high in the white community in Zimbabwe, and many patients develop several lesions of the same histological type during their lifetime. However, if basal cell carcinoma and squamous cell carcinoma of the skin occur in the same patient affecting the same or different sites, they are recorded separately (Curado MP et al., 2008).

3.1.6.4 Bulawayo registry structure and methods

This cancer registry was founded in 1963 and functioned for 15 years until 1978. It was located at Mpilo Central Hospital (MCH), Bulawayo, which is a large regional hospital acting as a referral centre for the south-western part of Zimbabwe (at that time called Rhodesia).

New cases of cancer were notified to the registry from all hospital wards and departments, pathology laboratories, and the mortuary. Direct notification from other sources was unusual. As MCH is the only hospital in the region with specialist cancer services, people with cancer diagnosed in the Bulawayo area were almost invariably

referred there for treatment, and thus captured in the registration network. Notification was a routine hospital procedure. All hospital case notes with a diagnosis or suspected diagnosis of cancer were sent to the registry on discharge or death. Copies of all histology and autopsy reports were submitted by both hospital and private laboratories. Death certificates were scrutinized monthly by the registrar; however, initial notification from this source was rare, and if it occurred an attempt was made to obtain all information about the case before registration, in particular details of age and place of residence.

3.1.7 Kyadondo County Cancer Registry (Uganda)

3.1.7.1 Registration area

The Kyadondo Cancer Registry collects data on the population of Kyadondo County, which includes the city of Kampala (the capital of Uganda), with its peri-urban areas and an area extending 30 km to the north. This population, which is mainly urban (80%), is composed of the Ganda ethnic group (50%) and other ethnic groups (30%). There are also immigrants from neighbouring countries, particularly from Kenya and Rwanda. Europeans, Asians, and other nationalities make up 1% of the population. The major activities of the residents of the capital include administration, trade, professional and para-professional activities, personal services, and plant and machine operation. There are no major industries in the county; subsistence farming is carried out on the outskirts of the capital. About 50% of the population are Catholic, 30% Anglican, 15% Muslim, and 5% of other religions. Staple foods consumed by the population of Kyadondo County include matoke (steamed green banana), posho (maize bread), beans, and groundnuts. About 50% of the city dwellers receive chlorine-treated piped water from the freshwater Lake Victoria (Curado MP et al., 2008).

3.1.7.2 Cancer care facilities

Kyadondo County is served by a 900-bed national referral hospital, Mulago Hospital, which is well equipped with modern diagnostic facilities. Mulago, which is also a teaching hospital for Makerere University Faculty of Medicine, is well supplied with consultants and teaching staff in all disciplines of medicine. An oncology unit involved in chemotherapy for various types of cancer and a radiotherapy unit are attached. The county has three other

missionary hospitals with 100 beds each. The Uganda Hospice provides services for the care of terminal cases of cancer in addition to other terminal diseases. Two private histopathology laboratories provide additional histological data to the registry (Curado MP et al., 2008).

3.1.7.3 Registry structure and methods

The Kampala Cancer Registry is situated in the Department of Pathology, Faculty of Medicine, Makerere University. Personnel include a pathologist director, a cancer registrar, and an assistant cancer registrar. All are employees of Makerere University. However, in various hospitals and units the registry has recruited personnel to assist in coordinating data collection. Submission of data to the registry is voluntary, as cancer is not a notifiable disease, and registration is almost entirely active. Doctors report a few cases to the registry directly. For hospitals, hospices, and histopathology laboratories, the registrars visit at least once a month and consult the hospital records, which include admissions and discharge registers, clinical notes, and pathology reports. For each case, both demographic and cancer diagnostic data are sought. Certification of death is only carried out for legal reasons and is very incomplete, so death certificates are not used as a source of information. The registry is computerized, and data management is carried out using the IARC/IACR CanReg software, which includes checks for consistency and validity and permits a search for potential duplicate registrations. Patient confidentiality is ensured by using only registration numbers during analysis of data. The registry is off limits to unauthorized persons (Curado MP et al., 2008).

3.1.8 Quality of cancer incidence data

The cancer incidence data used for the geographical comparison of the incidence of AIDS-related cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) in Africa for the period 1998–2002 were from the registries of Setif, Gharbiah, Sousse, Harare and Kyadondo County which appeared in Volume 9 of Cancer Incidence in Five Continents (CI5), published by IARC (Curado MP et al., 2008) in 2007 (Table 2). CI5 gathered data from 60 countries (225 registries) between 1998 and 2002, among them five African countries: Algeria, Egypt, Tunisia, Uganda, and Zimbabwe. Only cancer registries with data of sufficient quality are included in CI5. A number of criteria must be

met by registries to appear in this database, including a high proportion of tumours cases for which the diagnosis was histologically or microscopically verified (MV) and a small proportion of cases identified by death certificate only (DCO). Data from the Setif, Harare, and Kyadondo County registries were published in several previous volumes of CI5, which attests to the relatively high quality of data from these registries for several decades (2012).

Table 2: Data quality (percentage of microscopically verified [MV] and death certificate only [DCO] cases) for incidence of Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer in five population-based cancer registries in Africa, according to sex, for the period 1998–2002.

	Kaposi sarcoma (C46)		Non-Hodgkin lymphoma (C82-85.96)		Cervical cancer (C53)	
Registry	MV(%)	DCO(%)	MV(%)	DCO(%)	MV(%)	DCO(%)
Women						
Setif (Algeria)	100	0	100	0	95.2	0
Gharbiah (Egypt)	100	0	91.2	4.0	98.2	0.9
Sousse (Tunisia)	100	0	100	0	100	0
Harare (Zimbabwe)	55.6	12.5	82.1	8.4	72.5	7.0
Kyadondo County (Uganda)	76.6	0	75.0	0	59.2	0
Men						
Setif (Algeria)	100	0	100	0	–	–
Gharbiah (Egypt)	100	0	93.1	1.7	–	–
Sousse (Tunisia)	100	0	98.6	0	–	–
Harare (Zimbabwe)	59.7	11.4	87.9	6.9	–	–
Kyadondo County (Uganda)	74.3	0	76.0	0	–	–

Time trends of KS incidence were analyzed using incidence data from the registries of Bulawayo (Zimbabwe) for 1963–1971, Harare (Zimbabwe) for 1990–2005, and Kyadondo County (Uganda) for 1960–1971 and 1991–2007.

The percentage of MV cases of KS was 99.0% in Harare and 77.0% in Kyadondo County for the period 1990–1993, and 64.7% in Harare and 75.0% in Kyadondo Country for the period 2002–2007. The percentage of cases of KS identified by DCO was 0% in both populations for the period 1990–1993 and 9.4% in Harare and 0% in Kyadondo County for the period 2002–2007 (2012). In Bulawayo, death certification before burial period (1980-1983) was mandatory and the bodies of all people dying outside a hospital in the

African townships of the city were brought to the mortuary for autopsy before certification. In 1963–1967, autopsy rates were reported as 82.8% of all deaths in Bulawayo (Skinner et al., 1993).

3.2 Hospital-based data sources

A retrospective study on “The burden of human immunodeficiency virus (HIV)- and hepatitis C virus (HCV)-related cancers in Algeria” was conducted during my thesis work (2009–2013). I wondered whether the increase in HIV/AIDS prevalence rates in northern Africa has been followed by the emergence of AIDS-related cancers. Furthermore, after describing the geographical patterns of NHL in Setif, Gharbiah, Sousse, Kyadondo County, and Harare, we observed that in Egypt, where HIV/AIDS prevalence is low, NHL incidence was the highest. In 2009, the IARC Monograph Working Group assessed and confirmed the relationship between NHL and HCV (Bouvard et al., 2009). The observed highest rate of NHL in Egypt may be explained by this relationship because in Egypt, HCV prevalence is the highest in the world. I wanted to explore what happened in another northern African country with a low HIV/AIDS prevalence rate. I chose to study Algeria because there are more infected HIV/AIDS patients in Algeria than in other northern African countries (UNAIDS WHO, 2010). Furthermore, among the three northern African countries included in the description of the geographical pattern of AIDS-related cancers, Algeria has the second-highest HCV prevalence, after Egypt.

I identified possible Algerian collaborators and contacted them to find out who would like to work with me. I contacted the seven Algerian infectious disease services that confirm HIV diagnosis and follow up HIV-positive patients. Among them, those of Annaba and Oran agreed to work with me. In parallel, I contacted the four haematology services that treat NHL in eastern Algeria, where the HCV prevalence seemed to be the highest in the country (Sari, 2009). Among them, those of Annaba and Batna agreed to work with me.

I developed the research protocol and the questionnaires to collect individual data from the infectious disease services of the CHUs of Annaba and Oran and the haematology services of the CHUs of Annaba and Batna. During multiple research visits to Algeria, I supervised the data collection and the interview of patients. From the infectious disease service of the CHU of Annaba, my co-workers collected data by completing

questionnaires using HIV/AIDS patient medical records in paper format from the period 1988–2010. Furthermore, I entered the information from the questionnaires into an Excel table. Unfortunately, because of an archiving problem with the records of 1700 HIV-positive patients in the infectious disease service of the CHU of Oran, there were missing records, and sometimes patients with incomplete information were classified in the patient record of another patient. Furthermore, data were missing in the records and in the completed questionnaires; for these reasons, these data from the CHU of Oran were not used for the analysis.

From the haematology services of the CHUs of Annaba and Batna, my co-workers collected data by completing questionnaires using NHL patient medical records in paper format from the period 2009–2010. I also coordinated with laboratory scientists and supervised serum collection in HCV-positive patients affected by NHL treated at the CHU of Batna, and arranged shipment of these samples from the CHU to Lyon, France, for HCV genotyping at Hospices Civils de Lyon. It was not possible to contact HCV-infected NHL patients from the haematology service of Annaba.

3.2.1 Haematology services of Annaba and Batna University Hospital Centres

In Algeria, there are 14 haematology services distributed in 10 cities in north-western, northern, and north-eastern Algeria. Those of Annaba and Batna are in north-eastern Algeria (Société Algérienne d'Hématologie et de Transfusion Sanguine, 2013). These services cover five and nine wilayas (administrative divisions), respectively: Annaba, Skikda, El Taref, Guelma, and Souk Ahras; and Batna, Khenchla, Biskra, Msila, Mila, Oum El Bouaghi, El Oued, Tebessa, and Ouargla (Figure 7). However, they accept all patients whatever their address. In 2008, the population coverage of the Annaba and Batna haematology services was 2 837 150 and 6 953 209 people, respectively (2008 Algerian census).

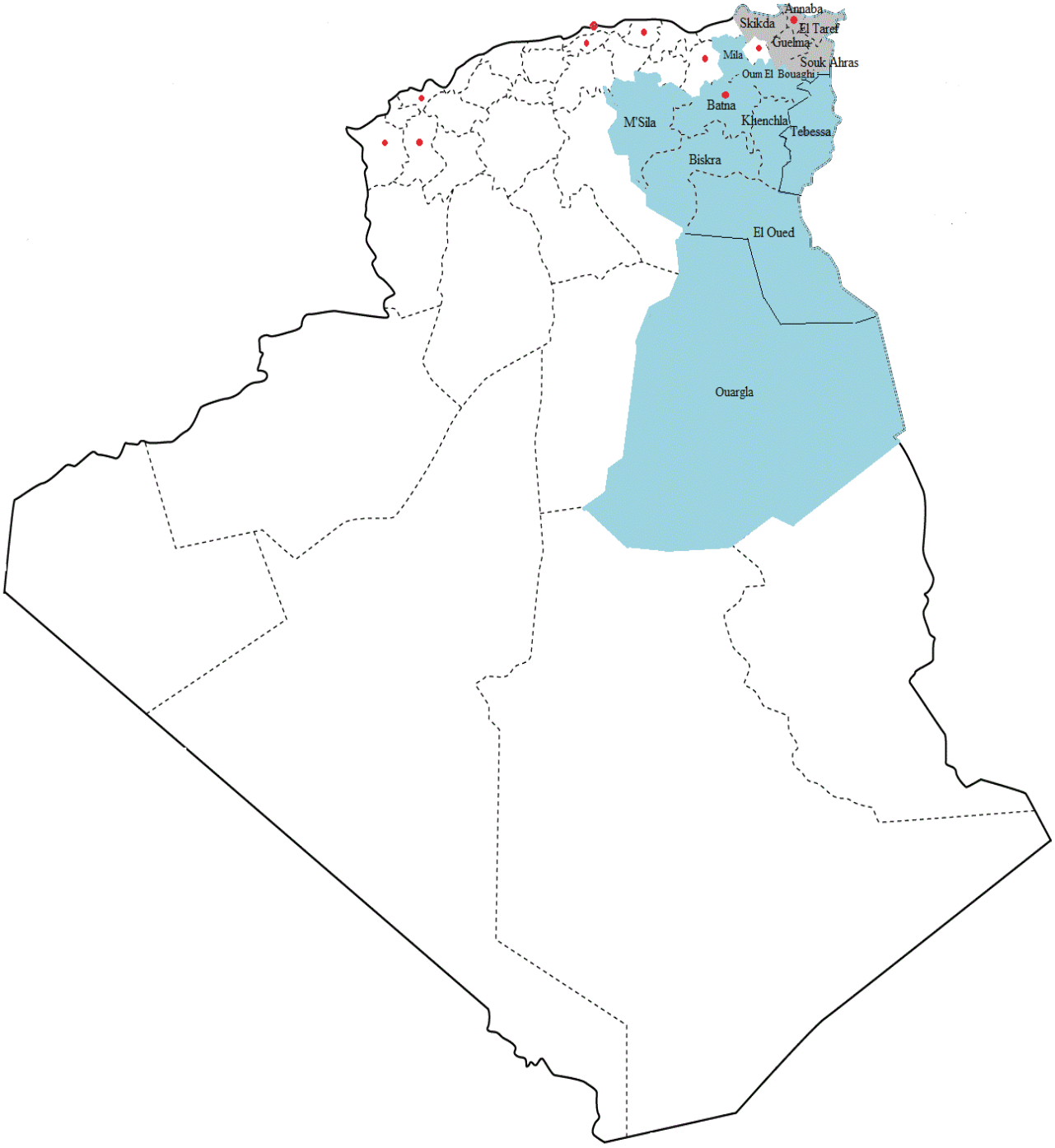
I was interested in NHL patients admitted and followed up at these haematology services between January 2009 and December 2010. Demographic information, serology (HIV, HCV, and HBV) and cancer status of patients with NHL were sought. Questionnaire 1 (Annex 1), which was used to record data on clinical characteristics of

patients, was completed using patient medical records. Risk factors for viral transmission (intravenous drug use, unprotected sex, tattooing, dental care, blood transfusion, dialysis, surgery, etc.) were also sought, using Questionnaire 2 (Annex 2). To complete this second questionnaire, patients were interviewed in person or by telephone when they were positively diagnosed with an infection. During the study period, the number of patients with co-occurrence of NHL and HCV infection was found to be three in Annaba and two in Batna (see Chapter 4.2). For genotyping of HCV, serum samples were collected in Batna from those patients with lymphoma and HCV infection and saved in the haematology service of CHU of Batna according to the following protocol:

1. Spin blood at 1200g for 10 min.
2. Aliquot 1 ml into labelled cryovials.
3. Place into dry ice to snap-freeze.
4. Transfer to –80 oC freezer.

Then, the samples were sent for analysis in the virology laboratory at Croix Rousse Hospital of Hospices Civils of Lyon, France.

Figure 7: Location of the Algerian haematology services (red dots), and population coverage areas of the haematology services of Annaba (grey area) and Batna (blue area)



3.2.2 STI/HIV/AIDS Reference Centre of Annaba

The Algerian health ministry (MSPRH/Ministère de la Santé, de la Population et de la Réforme Hospitalière) implemented seven centres for STI/HIV/AIDS ("Centres de Références des IST/VIH/SIDA"):

- EHS El HADI FLICI (ex El Kettar) Algiers,
- Hôpital Central de l'Armée, Algiers,
- CHU Annaba,
- CHU Constantine,
- CHU Oran,
- CHU Setif,
- Secteur Sanitaire Tamanrasset.

These centres structures were established in 1998 and are situated in infectious disease services of these hospitals. Their objective is to follow up people with HIV/AIDS, by performing:

- Screening for STI and HIV/AIDS,
- Clinical, psychological, and social management of people with HIV/AIDS,
- Clinical management of opportunistic disease.

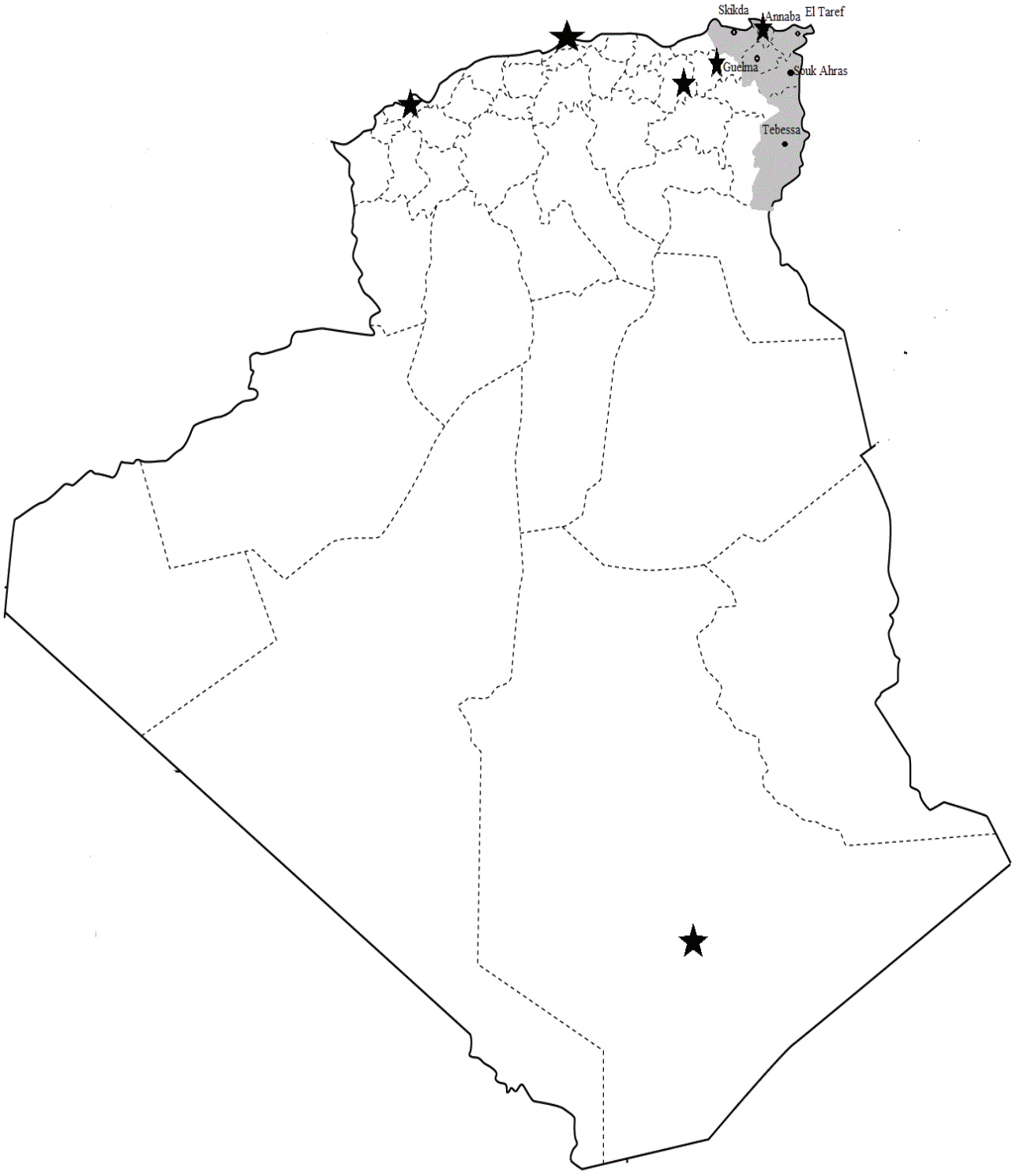
All Algerian and foreign persons diagnosed HIV/AIDS positive and living in Algeria are followed up in one of these seven centres. They receive free highly active antiretroviral treatment (HAART) if they meet the criteria for initiating HAART. Guidelines for the management of HIV and AIDS were published in 2006 and in 2010 (Comité de rédaction de la Direction de la Prévention, 2010). According to these guidelines, HAART can be started among symptomatic (weight loss >10 kg, continuous diarrhoea or fever, "stage C" according to the 1993 CDC classification [(CDC staff members, 1993)], oropharyngeal candidiasis, etc.); asymptomatic (CD4+ T-lymphocyte counts <350 cells/mm3 [2006 guidelines] and then 500 cells/mm3 [2010 guidelines] during exams performed at least 1 month apart) and some specific patients (pregnant women, HIV-discordant couples, children <2 years old, patients with HBV and/or HCV co-infections, with cardiovascular risks, >50 years old, etc.). Triple therapy has been used in Algeria, using two nucleoside reverse transcriptase inhibitors (such as zidovudine [AZT], abacavir [ABC] and/or lamivudine [3TC]) and one non-nucleoside reverse transcriptase inhibitor (efavirenz or

nevirapine) for first-line treatment. In case of failure of the first-line treatment, at least two molecules are changed: the non-nucleoside reverse transcriptase inhibitor is replaced by a protease inhibitor (ritonavir, atazanavir, lopinavir/ritonavir or darunavir), and one nucleoside reverse transcriptase inhibitor is replaced by another (tenofovir or emtricitabine). No therapeutic approach is currently validated for third-line treatment.

HIV/AIDS data were obtained from the infectious disease service of the CHU of Annaba, which has been the only service in the region specialized in infectious disease. It was founded in 1988, and since 1998 it has also been one of the seven reference centres for STI/HIV/AIDS in the country. This infectious disease service covers six north-eastern wilayas (administrative divisions): Annaba, El Taref, Skikda, Tebessa, Souk Ahrass, and Guelma (Figure 8). However, this service accepts all patients whatever their address. In 2008, the population coverage was 3 485 841 people (2008 Algerian census). Individuals in the Annaba area diagnosed with HIV/AIDS were almost invariably referred to this service for treatment and follow up, and thus captured in the registration network.

A part of the thesis work focused on HIV/AIDS patients admitted and followed up at the infectious disease service of the CHU of Annaba between January 1988 and December 2010. Demographic information, serology, and cancer status of patients with HIV/AIDS and who had received HAART were sought. Questionnaire 3 (Annex3) was completed using patient medical records. We were looking for cancer emergence up to the end of 2011. Clinical observations were noted from records of those patients living with HIV/AIDS and affected by cancer.

Figure 8: Location of the Algerian STI/HIV/AIDS reference centres (stars) and population coverage of that the STI/HIV/AIDS Reference Centre of Annaba (grey area)



3.2.1 Ethical and consent issue of named data

The research participants in the descriptive and retrospective study on 'The burden of human immunodeficiency virus (HIV)- and hepatitis C virus (HCV)-related cancers in Algeria' were identified as patients who visited the infectious disease services of the CHUs of Annaba and Oran and the haematological services of the CHUs of Annaba and Batna, all in Algeria. All HIV-positive patients diagnosed and followed up in these infectious disease services between 1988 and 2010, and all patients with NHL diagnosed and followed up in these haematological services between 2009 and 2010, were recruited.

Because no ethical committees existed in the CHUs involved in the study, the heads of the services were responsible for ethical review, and they fully approved the project. The participants did not receive any payments, reimbursement of expenses, or any other benefits or incentives for taking part in this research.

Neither HIV-positive patients in the infectious disease services of the CHUs of Annaba and Oran nor patients with NHL from the haematological services of the CHUs of Annaba and Batna were approached, with the exception of two HCV-positive patients with NHL, who were approached for the transmission route investigation and the serum sample collection. These two patients, from the CHU of Batna, were approached by their personal physician to request a face-to-face or telephonic interview using a questionnaire (Annex 2). Apart from these two interviews, patient medical records were used to retrieve the data sought.

A serum sample from one of the two HCV-positive patients with NHL was collected by a nurse working in the haematological service of the CHU of Batna, in order to genotype the virus. This collection of a serum sample was performed during a previously scheduled patient visit. This study did not change the schedule of patient care visits. This clinical procedure, to obtain a sample of human biological material, should have been done as a part of the routine clinical care to treat HCV infection. Unfortunately, for economic reasons it was not done. The second HCV-positive patient with NHL refused this procedure.

Informed and voluntary consent was requested in Arabic from the two persons approached for the transmission route investigation and the serum sample collection. They were informed about the purpose and nature of the study, what participation would

require them to do, and what benefits are intended to result from the study. The information provided to the patients included a description of how communication would be handled (e.g. case report).

The examination of patient medical records and completion of the questionnaires (Annexes 1, 2, and 3) were performed by those personnel who would normally have access to these records (physicians and nurses). The initials and record number of each patient were noted on the questionnaires to allow the medical professionals to find the patient's records again, if necessary. This work was performed under my supervision, and I participated in keying in the information available in the questionnaires. I have stored and have had control of the anonymous data generated by the study. The analysis of the data from the study took place in the Cancer Information Section of the International Agency for Research on Cancer and was undertaken by me. The head of the services, my supervisors, and I have access to the data. The specimen was stored in the haematological service of the CHU of Batna until shipment to Lyon, where it was transferred directly to Hospices Civils de Lyon for genotyping. After the genotyping of HCV, the serum sample was destroyed. The sample was identified by the initials and the record number of the patient; the identification of the patient could be done only by the head of the haematological service of the CHU of Batna.

The scientific quality of the research was assessed through internal review (my supervisors and participating colleagues) and by my thesis committee, with which I discussed the study in Algeria. I was in charge of monitoring and auditing the conduct of the research. I checked whether the records were correctly archived to make sure that no patients had been missed. I checked whether the questionnaires had been completed correctly and the information keyed in correctly. I contacted the physicians to complete missing data when this was possible. The results of the study are presented in the current thesis manuscript. Furthermore, they are being disseminated through peer-reviewed scientific journals (one original article and two case reports).

This project was funded by the International Agency for Research for Cancer with an amount of 3000 euros. No payment or benefits in excess of the costs of undertaking the research were received by any researcher involved in this study

3.3 Statistics: definitions and analyses

3.3.1 HIV prevalence and incidence

HIV prevalence (or HIV/AIDS prevalence) among adults aged 15–49 years is defined by WHO as the percentage of people with HIV infection among all people aged 15–49 years. HIV prevalence data from surveillance systems, which may include national surveys with HIV testing, are used to estimate HIV prevalence using standardized methods of estimation developed by UNAIDS and WHO in collaboration with the UNAIDS Reference Group on Estimates, Modelling and Projections. For generalized epidemics, the Epidemic Projection Package software is used to fit a curve to empirical data points. For concentrated or low-level epidemics, a spreadsheet method is used that requires inputs on estimated population size and HIV prevalence in high risk populations (UNAIDS Reference Group on Estimates, 2002).

HIV incidence is defined by WHO as the number of new HIV infections in a population during a certain time period. This infection occurs at a time after a high-risk behaviour for HIV transmission.

The determination of HIV incidence in a population is important to:

- Monitor the epidemic,
- Improve the targeting of populations for interventions, and
- Evaluate the effectiveness of HIV prevention and treatment programs.

This is especially important in low- and middle-income countries, which continue to bear a disproportionate share of the global burden of HIV/AIDS. In addition, the identification of newly infected persons will allow for interventions to reduce the risk of HIV transmission.

Determining the best strategy for measuring incidence remains a challenge. Traditional HIV surveillance methods have used changes in measures of prevalence to estimate HIV incidence rates, but this approach requires multiple rounds of surveillance over many years in the same population groups. The prospective follow up of a cohort of HIV-negative persons provides a direct measure of HIV incidence; however, such studies are challenging and expensive, are not sustainable in resource-limited settings, and raise ethical issues. Furthermore, the enrolment of persons into a cohort study often leads to

behaviour changes that result in a lower observed HIV incidence than in the broader population of interest (UNAIDS, 2011a).

3.3.2 Cancer incidence and prevalence

Cancer occurrence is most appropriately measured in terms of incidence rates, for example as the number of newly diagnosed cases per 100 000 person-years of observation time (Breslow and Day, 1980). Unlike infections, patients with cancer become ill as a result of long processes that take several years. Thus, in the cancer field, cancer incidence is synonymous with the rate of newly diagnosed cancer.

Cancer prevalence is defined as the number of living people who have ever had a cancer diagnosis. It includes people diagnosed with cancer in the past as well those who were recently diagnosed. Cancer prevalence is determined by how often a cancer occurs (incidence) and by how long people normally live after diagnosis (survival). Prevalence counts are highest for the most common cancers with the longest survival. A common cancer with a shorter survival may have a lower prevalence count than a less common cancer with a longer survival. For example, although lung cancer is the most common cancer in the world in both men and women, the prevalence count for lung cancer is lower than that for NHL, which is the eighth most common cancer worldwide (IARC, 2011). This is because people survive longer with NHL than with lung cancer, so there are more people living after a diagnosis of NHL than after a diagnosis of lung cancer.

Note that in this thesis manuscript I will use the term “incidence” to mean “cancer incidence”.

3.3.3 Direct standardization of cancer incidence

For the cancer incidence of several populations to be compared, bias related to population age structure must be taken into account. There are two types of cancer incidence standardization: direct and indirect. Only the direct method is described here because it was used in the statistical analysis.

The age-standardized rate is a summary of the individual age-specific rates using an external population called a standard population. This is the incidence that would be observed if the population had the age structure of the standard population, and

corresponds to the crude incidence rate in the standard population. The age-standardized incidence rate (ASR) was expressed, as was the crude incidence rate, as the number of new cases per 100 000 person-years. We had accessed to the incidence stratified by 5-year age group (0–4; 5–9; ... ; 70–74; 85+) for the six African populations studied.

The calculation was a weighted average of age-specific rates:

$$ASR = \sum_{i=1}^{18} \frac{d_i w_i}{y_i}$$

where i represents the age group (of which there are 18), di is the number of cancer cases in the ith age group, yi is the population size in the ith age group, and wi is the weight applied for the ith age group; di/yi is the cancer age-specific rate for each ith category, and the sum of the wi is equal to 100 000 to express the cancer ASR per 100 000 person-years (Breslow and Day, 1980).

World and African standard populations (Dos Santos Silva, 1999) were used for standardization (Table3). The world standard population was used to allow comparisons with other published data, and the African standard population was used because its age structure is most similar to that of the African populations studied (Figure 10). Furthermore, the high-risk age group for HIV/AIDS is 15–49, so cancers related to HIV/AIDS are more likely to occur in this age group.

Tableau 3: African and World standard populations

Age group (years)	African	World
0	2 000	2 400
1–4	8 000	9 600
5–9	10 000	10 000
10–14	10 000	9 000
15–19	10 000	9 000
20–24	10 000	8 000
25–29	10 000	8 000
30–34	10 000	6 000
35–39	10 000	6 000
40–44	5 000	6 000
45–49	5 000	6 000
50–54	3 000	5 000
55–59	2 000	4 000
60–64	2 000	4 000
65–69	1 000	3 000
70–74	1 000	2 000
75–79	500	1 000
80–84	300	500
85+	200	500
Total	100 000	100 000

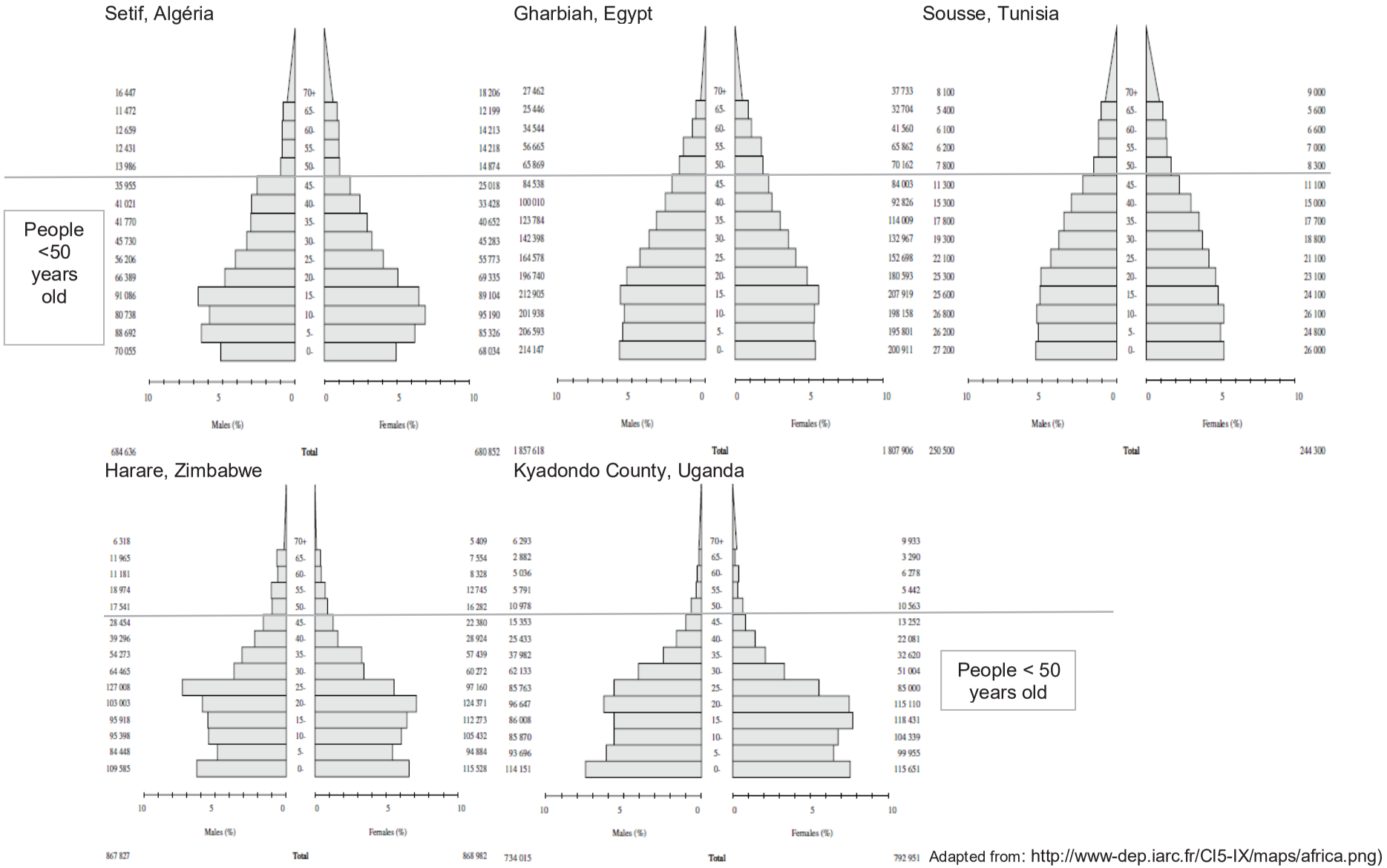
Number of people under 50 years old

90,000

80,000

Adapted from: Dos Santos Silva (1999)

Figure 9: African population age structures (1998-2002)



Adapted from: http://www-dep.iarc.fr/CI5-IX/maps/africa.png)

3.3.4 Comparative measure of incidence

Calculation of variance of ASRs

Variances of ASRs were used to assess the statistical significance of the difference between rates in population A and population B. We based the estimation of variance of ASRs on Breslow and Day's method, modified to use a binomial assumption (Keyfitz, 1966) for the variance of the crude age-specific rates:

$$Var(ASR) = \frac{\sum_{i=1}^{18}\left(\frac{d_i * (y_i - d_i) * w_i^2}{y_i^3}\right)}{\left(\sum_{i=1}^{18} w_i\right)^2}$$

Comparison of ASRs of population (or period) A with ASRs of population (or period) B

To identify significant changes in incidence between population (or period) A and population (or period) B, we estimated the comparative incidence figure (CIF), which corresponds to the ratio of the ASR in population A to the ASR in population B:

$$CIF = \frac{ASR_{\text{Population A}}}{ASR_{\text{Population B}}}$$

The upper (CI_u) and lower (CI_l) limits of the 95% confidence interval for CIF were computed using the following formula:

$$CI_{u/l} = e^{\ln(CIF) \pm 1.96 * \sqrt{\frac{Var(ASR_{\text{Population A}})}{ASR^2_{\text{Population A}}} + \frac{Var(ASR_{\text{Population B}})}{ASR^2_{\text{Population B}}}}}$$

We considered the difference between rates in population (or period) A and rates in population (or period) B to be significant if unity was not included in the 95% confidence interval of the CIF.

3.3.5 Comparative measure of all-cause mortality in HIV/AIDS patients

The standardized mortality ratio (SMR) was used to compare all-cause mortality in the HIV-positive patients from the STI/HIV/AIDS Reference Centre of Annaba to that in the general population of its coverage area. SMR compares the observed number of deaths in the HIV/AIDS patient cohort with an expected number obtained by applying the standard rates (all-cause mortality in the general population) to the cohort age structure.

$$SMR = \frac{O\ (\text{Observed number of deaths})}{E\ (\text{Expected number of deaths})}$$

The SMR is especially applicable where the two populations have dissimilar age distributions, and in cases where direct age-standardization may not be appropriate because the study population is small.

To determine a range of possible values of the true SMR, the 95% confidence interval for SMR was calculated; the upper and lower limits of the confidence interval of the SMR were derived from the standard chi-square test:

$$SMR_L = \theta_L = SMR\left[1 + \frac{1}{2D}Z^2_{\alpha/2}\left\{1 - \left(4D/Z^2_{\alpha/2}\right)^{1/2}\right\}\right]$$

$$SMR_U = \theta_U = SMR\left[1 + \frac{1}{2D}Z^2_{\alpha/2}\left\{1 + \left(4D/Z^2_{\alpha/2}\right)^{1/2}\right\}\right]$$

where D denotes the total observed number of deaths and Zα/2 denotes the 100(1 – α/2) percentile of the unit normal distribution. We did not use a continuity correction for this calculation, because doing so gives less accurate limits empirically (Breslow and Day, 1980).

3.3.6 Statistical tests

To test the null hypothesis that values in population subgroups are equal, we used Fisher's exact test to compare variances of categorical variables between subgroups and Student's t test to compare means of continuous variables between subgroups

Šidàk correction was used to counteract the problem of multiple comparisons and control the family-wise error rate because individual tests were assumed to be independent (Šidàk, 1967). Instead of using a p-value threshold of α = 0.05, a stricter threshold with was used. Here, n is the number of individual tests performed.

3.3.7 Time trend analysis: joinpoint model

The analysis of KS incidence time trends was performed using the joinpoint regression model for Uganda and Zimbabwe (National Cancer Institute, 2012). This method determines the most appropriate model to present changes in trends over time. The model identifies the points of inflection (joinpoints) in trends; these points are between two straight lines with distinct slopes. Kim et al. developed the procedure of joinpoint regression (Kim et al., 2000).

This technique has been used by the Surveillance Research Program of the U.S. National Cancer Institute, which has published free software called the Joinpoint Regression Program (version 3.0), a Windows-based statistical software package that computes and analyses non-linear, piecewise trends of time series.

The software fitted models to the data that allowed for testing of whether an apparent change in trend was statistically significant. The goal of the Joinpoint Regression Program is not to provide models that best fit the data, but models that best summarize the behaviour or the data trend across years.

The trend was computed in segments whose start and end were determined to best fit the data. These segments were connected together at joinpoints. If there were no joinpoints, the trend is flat and it was displayed as a straight line. I supplied the minimum and maximum number of points, 0 and 4, respectively. The program started with the minimum number of joinpoints (0) and fitted a trend line to the data. It tested whether more joinpoints were statistically significant and should be added to the model. It added these joinpoints, up to the maximum number specified, and displayed graphs of all models fit (i.e. graphs of the model with the minimum number of joinpoints up to the model with the maximum number of joinpoints).

If a by-variable was specified (e.g. sex, age group), the software allowed one graph of each model to be displayed per level of the by-variable. For example, if the by-variable was sex with levels male and female, then the software displayed, for each level of the by-variable sex, all the models (i.e. models with 0 to 4 joinpoints) fitted to the data.

The tests of significance used a Monte Carlo permutation method. The models might incorporate estimated variations for each point (e.g. when the responses are age-adjusted rates) or use a Poisson model of variation. In addition, the models might also be linear on the logarithm of the response variable.

The annual percentage change (APC) was estimated by fitting a simple linear model: the logarithm of the yearly age-adjusted rates was first regressed on time, and then a transformation of the slope was used to calculate the percentage change per year. The APC was easy to calculate and interpret. For long-term trend analysis, however, the linearity of rates on the logarithmic scale, implying a constant rate of change, might not apply over the entire time period of interest. While the joinpoint program computed the

trend in segments, it was thus useful to summarize the trend over a fixed, pre-determined time interval. The average annual percentage change (AAPC) was a method that used the underlying joinpoint model to compute a summary measure over a fixed, pre-specified time interval.

I applied a joinpoint regression model to describe KS and HIV/AIDS continuous changes and used the grid-search method to fit the regression function with unknown joinpoints, assuming constant variance for homoscedasticity and uncorrelated errors. I estimated the number of joinpoints using a log-linear model; the dependent variable was the KS incidence standardized on the African population in Zimbabwe and Uganda, and the SMR comparing HIV/AIDS mortality with that of Algerian general population; the independent variable was year as a continuous variable, and the number of inflection points ranged from 0 to 4. I found the number of significant joinpoints by performing several automatic permutation tests, each of which had a correct significance level asymptotically. Each p-value was found using Monte Carlo methods.

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4 Results

4.1 Geographical patterns of Kaposi sarcoma, non-Hodgkin lymphomas, and cervical cancer associated with HIV infection in five African populations

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This is a corrected version of the published original article. The words in grey have been added in the original text and the barred words are those which have been dropped from the original text.

4.1.1 Abstract

The objective of this study is to describe the most recent geographical patterns of incidence of AIDS-related cancers, Kaposi's sarcoma (KS), nonHodgkin lymphoma (NHL), and cervical cancer in North African and subSaharan African populations. Data were extracted for the period 1998–2002 from five African population-based cancer registries: Kyadondo, Harare, Setif, Sousse, and Gharbiah. Age-standardized rates were calculated using the African standard population; a comparison was made between these populations by computing the ~~standardized incidence ratio~~ comparative incidence figures and 95% confidence intervals. The KS rate was found to be significantly higher in men than in women, and higher in Harare (women: 26.3/100,000; men: 50.4/100,000) and Kyadondo (women: 23.6/100,000; men: 30.2/100,000) than in the North African sites for both sexes (<0.3/100,000). In addition, the KS rate in women from Harare was similar to that of Kyadondo. Gharbiah presented the highest rates for NHL (women: seven per 100,000; men: 11.9/100,000) for both sexes. We observed that Harare and Kyadondo had similar age-specific incidence in the high-risk age group for HIV/AIDS (15–49 years), and these rates were 4.5-fold higher in subSaharan populations than those in the North African sites. Thus, it was observed that the pattern of HIV prevalence is variable with the lowest prevalence in North African countries, intermediate prevalence in Uganda, and the highest prevalence in Zimbabwe. Our findings show that the incidence of NHL and cervical cancer, considered to be HIV/AIDS-related cancers, does not follow the pattern of HIV prevalence in the five studied African populations. Thus, the highest NHL incidence rate in both sexes in Egyp may be explained, at least in great part, by the highest hepatitis C virus prevalence observed there. Indeed, factors other than HIV infection likely contribute to their geographical patterns.

4.1.2 Introduction

Cancer remains a significant burden for HIV-infected individuals. AIDS-related cancers are more likely to occur in people infected with HIV, the most common being Kaposi's sarcoma (KS), nonHodgkin lymphoma (NHL), and cervical cancer (Mbulaiteye et al., 2006; National Cancer Institute, 2010). Hodgkin lymphoma and the cancers of the anus and the conjunctiva are three other cancers that have been newly classified as AIDS-related cancers by the International Agency for Research on Cancer Monographs Working group. HIV has an indirect effect on the emergence of these cancers. Indeed, the etiologic virus for KS is human herpes virus 8 (HHV-8); for cervical cancer is human papillomavirus (HPV); and for NHLs are Epstein–Barr virus (EBV), HHV-8, hepatitis C virus (HCV), and human T-cell lymphotrophic virus type 1 (Bouvard et al., 2009).

Most studies on AIDS and cancer have been carried out in the United States, Europe, and Australia. Compared with the general population, the risk of developing KS increased, by more than 106 000 times, among men who were homo- or bi-sexual with HIV/AIDS and, by more than 13 000 times, among people who were nonhomo- or bi-sexual with HIV/AIDS (Biggar et al., 1996). NHL frequency was increased to up to 60–200-fold in patients who were HIV positive (Beral et al., 1991). The widespread use of highly active antiretroviral therapy (HAART) has led to a decrease in mortality due to AIDS; a decline in the incidence of KS and NHL has also been observed in industrialized countries since 1996. However, the incidence of cervical cancer does not appear to be changing since the introduction of antiretroviral therapy (ART) (Palefsky, 2009; Polesel et al., 2010).

Very few scientific publications have addressed cancer and HIV/AIDS in North African countries. It may be interesting to observe these cancers in Africa, which consists of two disparate regions: subSaharan Africa, with the highest rates of HIV/AIDS in the world, and Northern Africa, with the lowest rates of HIV/AIDS in the world. A recent study that focused on subSaharan Africa showed a clear association between KS and NHL and HIV infections; however, a weaker association was identified for cervical cancer (Sasco et al., 2010). Therefore, further studies on the impact of HIV/AIDS and cancer on African

populations are needed. In Africa, during the period 1998–2002, ART coverage was low (2%) (WHO, 2010). Thus the impact of ART may not have been well observed, and we hypothesized that our study was performed before the availability of ART.

We aimed to describe the geographical patterns of the incidence of three AIDS-related cancers (KS, NHL, and cervical cancer) in the period 1998–2002, in North African and subSaharan African populations.

4.1.3 Methods

4.1.3.1 Data source

We performed an ecological study using grouped cancer incidence data extracted from two subSaharan and three North African population-based cancer registries : Kyadondo County (Uganda), Harare (Zimbabwe), Setif wilaya (Algeria), Central Region of Tunisia, and Gharbiah Governorate (Egypt). These cancer registries were all included in the publication Cancer in Five Continents (CI5), volume IX (Curado et al., 2008).

The overall population coverage for these five registries was 6.3 million in 2002 (0.7% of the African population): Harare (Mashonaland East province, north-east Zimbabwe) with 1.7 million (16.4% of national population), Kyadondo County (covering Kampala, the capital city, and part of the Wakiso district in Uganda) with 1.2 million (3.0% of national population), Setif (wilaya situated in East Algeria) with 1.3 million (4.3% of national population), the Central Region of Tunisia (which includes the provinces of Sousse, Monastir, Mahdia, Kairouan, Kasserine, and Sidi Bouzid) with 0.49 million (~~28.5%~~ 18.5% of national population), and the Gharbiah Governorate (in the west and center of the Delta region in Lower Egypt) with 2.9 million (5.7% of national population).

The percentage of microscopically verified (MV) cancers was almost 100% for all sites in the three North African populations, whereas this value was lower in subSaharan populations (yet always above 50%), suggesting a better validity of data from North African registries. The percentage of cases included from death certificates only (DCO) was low, the maximum value being observed in Zimbabwe for KS, with 12.5% of incident cancers. A low DCO% may indicate efficient case-finding, but it could also result from the efficient traceback of death certificate notification cases. Nevertheless, an elevated DCO% is suggestive of incompleteness. However, in Africa, data on death certificate are often limited due to the lack of a legal obligation to indicate the cause of death, and therefore most data from the cancer registries come from incident cases (Curado et al., 2008).

The cancer site definition was based on the International Classification of Diseases for Oncology 10 (Fritz et al., 2010; Percy et al., 2010) as follows: KS (C46), NHL (C82–85, C96), cervical cancer (C53).

4.1.3.2 Statistical analyses

Cases with unknown age were excluded because the percentage of these cases represented less than 1% of those with NHL and cervical cancer, and for KS it was 5 and 3.5% for men and women, respectively. We calculated the age-standardized incidence rates (ASR) for the three selected AIDS-related cancer sites for the period 1998–2002 for each sex in the five populations. Eighty percent of the African standard population and 70% of the world standard population were under the age of 50 years. As we compared African populations, at least 75.5% of the North African populations and 83% of the subSaharan populations studied were under the age of 50 years; age standardization was performed by the direct method using the African standard population, which more closely fit the age distribution of the populations studied than did the world standard population (Dos Santos Silva, 1999).

To identify significant differences between two populations, we estimated the comparative incidence figure (CIF) that corresponds to the ratio of the ASRs in these populations. The 95% confidence interval (CI) of the CIF was also computed (Curado et al., 2008). We considered the CIF to be significant when its 95% CI did not contain the value 1.

All statistical analyses were carried out using Statistical Analysis System software, version 9.2 (SAS Institute, Cary, North Carolina, USA).

4.1.4 Results

4.1.4.1 Kaposi's sarcoma

Incidence rates were higher in Harare (26.3/100,000 for women and 50.4/100,000 for men) and Kyadondo County (23.6/100,000 for women and 30.2/100,000 for men) than in North African sites for both sexes (<0.3/100,000) (Figures 11 and 12). Age-specific incidence rates of KS in Harare and in Kyadondo were the highest among the age groups of 30–39 years and of 40–49 years in both sexes (Figure 13).

The ASR for KS in men from Harare was significantly higher than from Kyadondo [CIF=1.7; 95% CI (1.5–1.8); p-value<0.001]; however, rates were similar in women. With regard to sex, ASR (Africa standard) for KS was higher in men than in women in Harare and was similar in both genders in Kyadondo, as shown by the ~~sex ratios 1.9 : 1 and 1.3 :~~

4 the CIFs 1.9, 95% CI (1.7;2.1); p-value=0.03; and 1.3, 95% CI (1.1;1.4), p-value=0.95, respectively.

Figure 10: Geographical pattern of the ASR (African standard population, per 100,000) of KS and NHL in five African populations, Male, 1998–2002.

Figure 11: Geographical pattern of the ASR (African standard population, per 100,000) of KS, NHL and cervical cancer in five African populations, Female, 1998–2002.

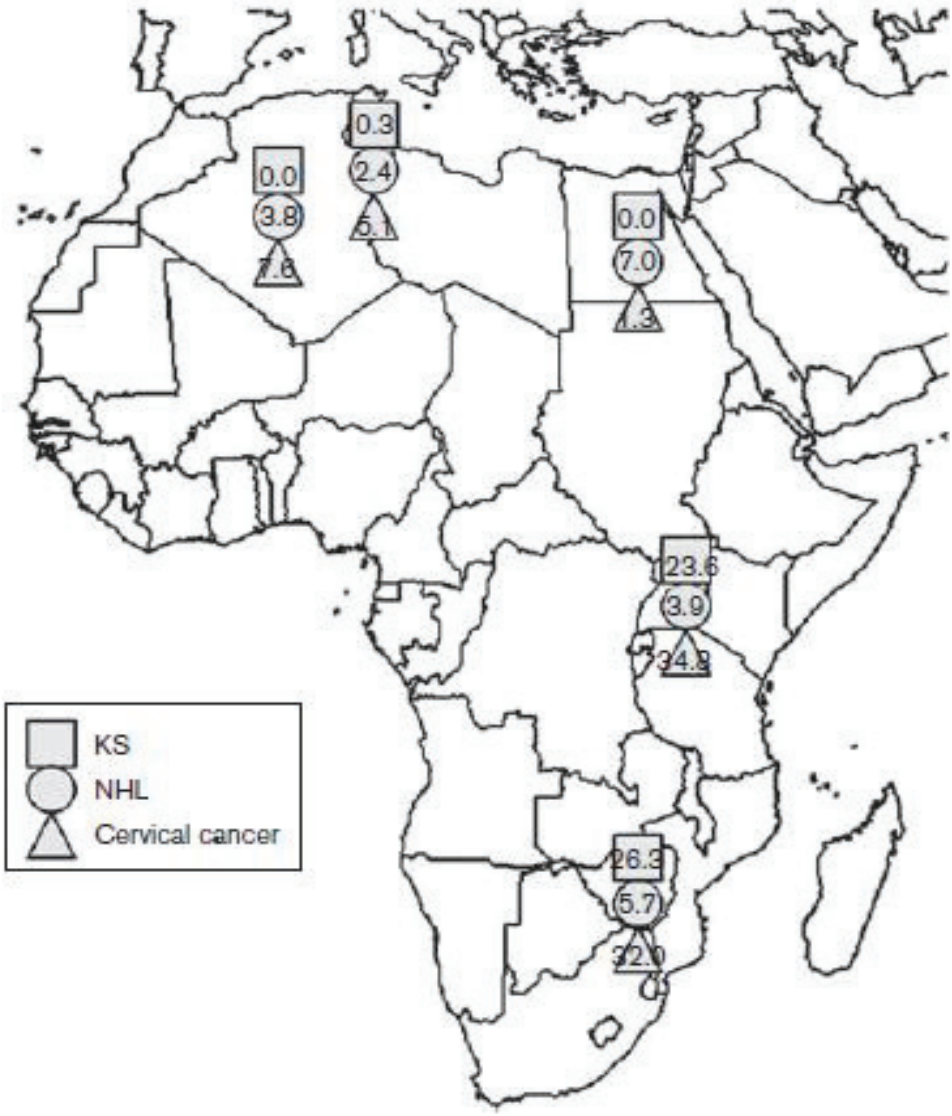
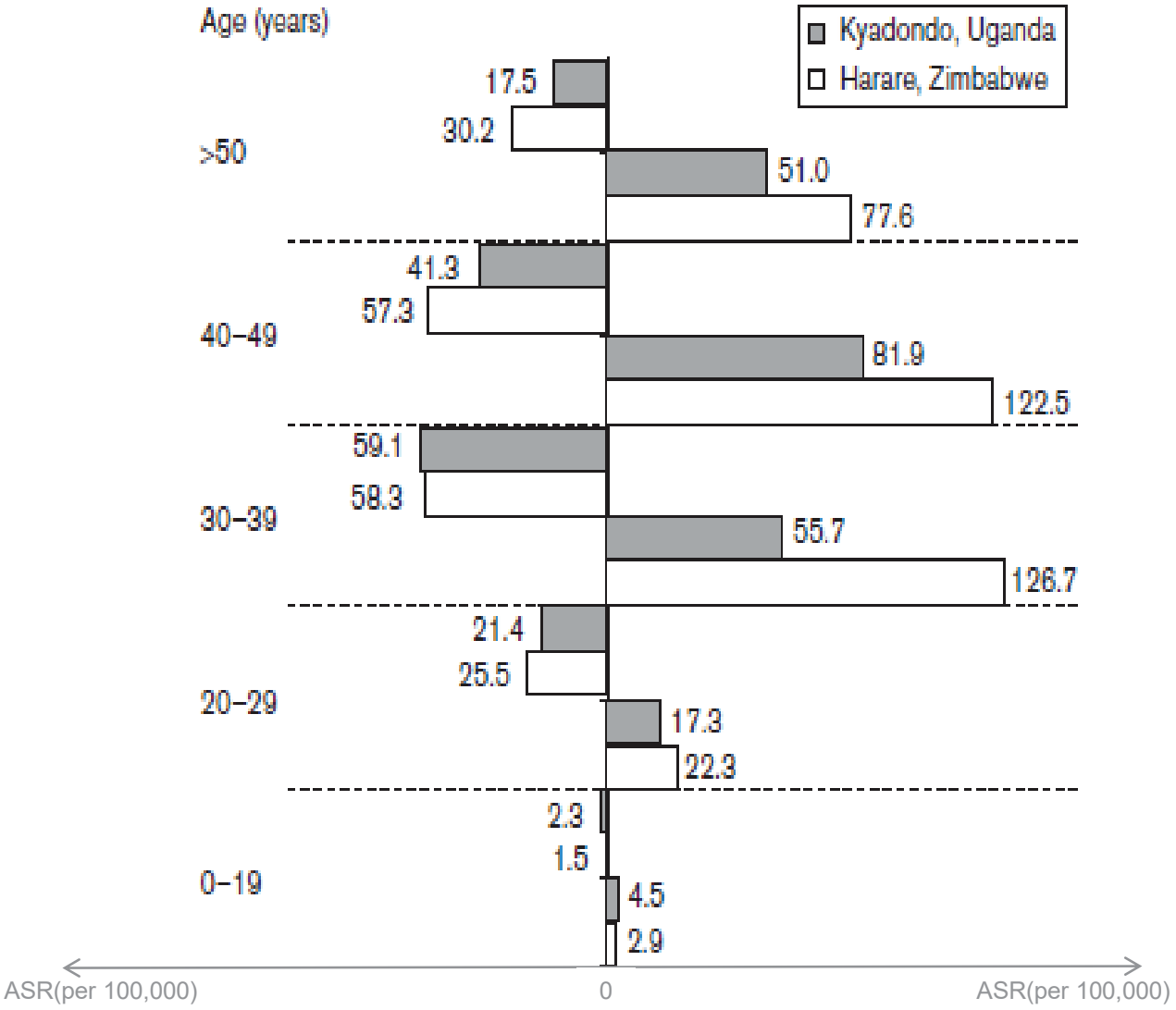


Figure 12: Age-Specific incidence (per 100,000) of Kaposi sarcoma in Harare and Kyadondo, in women (left side) and men (right side)1998–2002 (per 100,000).



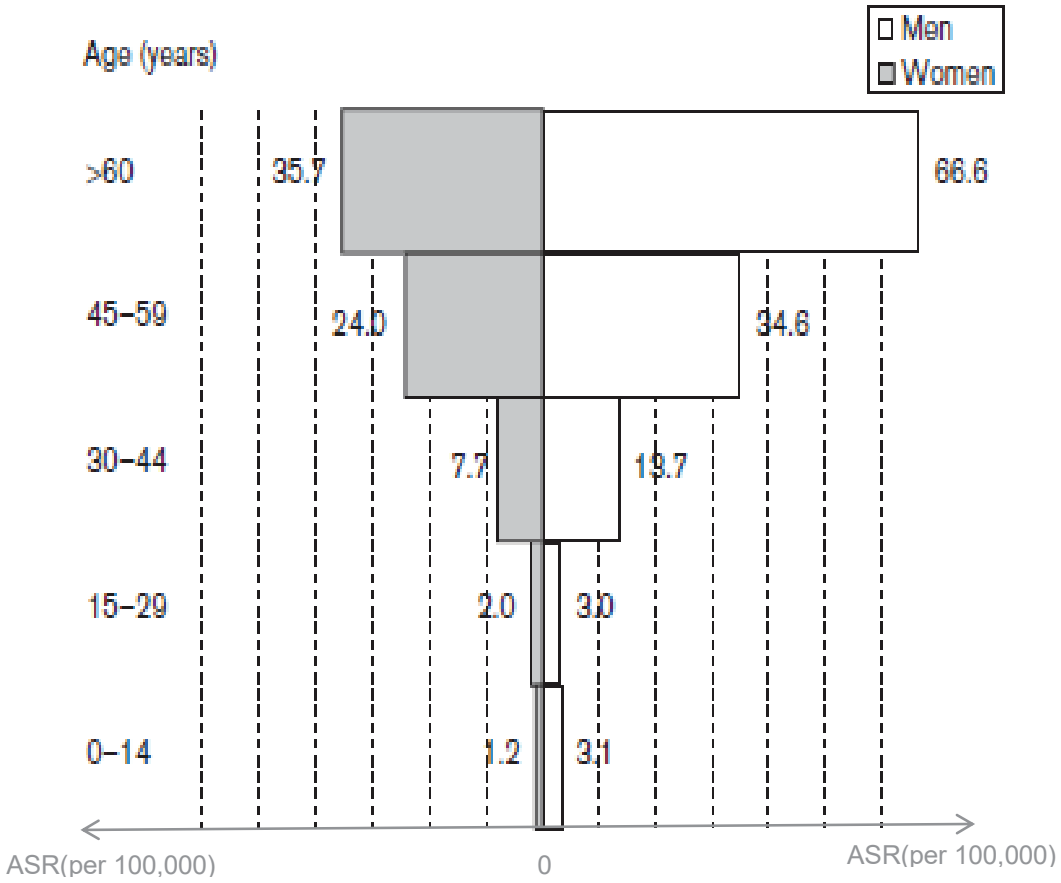
4.1.4.2 NonHodgkin lymphoma

Gharbiah presented the highest ASRs in the five populations studied (seven/100 000 for women and 11.9/100,000 for men; p-values<0.001); ~~however, these rates were not significantly higher than rates from Harare~~ (Figures 11 and 12). The lowest rates were observed in the two other North African populations in women (central region of Tunisia: 2.4/100,000 and Setif: 2.7/100 000), and in men in Setif and in Kyadondo (Setif: 3.8/100,000 and Kyadondo: 4.8/100 000). NHL rates were similar ~~more frequent~~ in men

~~than~~ in women in all populations studied (p-values not significant)~~Ghabiah: 1.7 : 1, Setif 1.4 : 1, Sousse: 2.2 : 1, Harare: 1.3 : 1, and Kyadondo: 1.4 : 1~~).

In Gharbiah, age-specific incidence rates increased with age and were higher in men than in women (Figure 14). Indeed, at ages over 60 years, NHL incidence was 1.9-fold higher in men than in women. Kyadondo had the highest NHL ASR (Africa) of all registries for children (age group: 0–14).

Figure 13: Age-specific incidence of non-Hodgkin lymphoma in Gharbiah, Egypt, 1998–2002 (per 100,000).

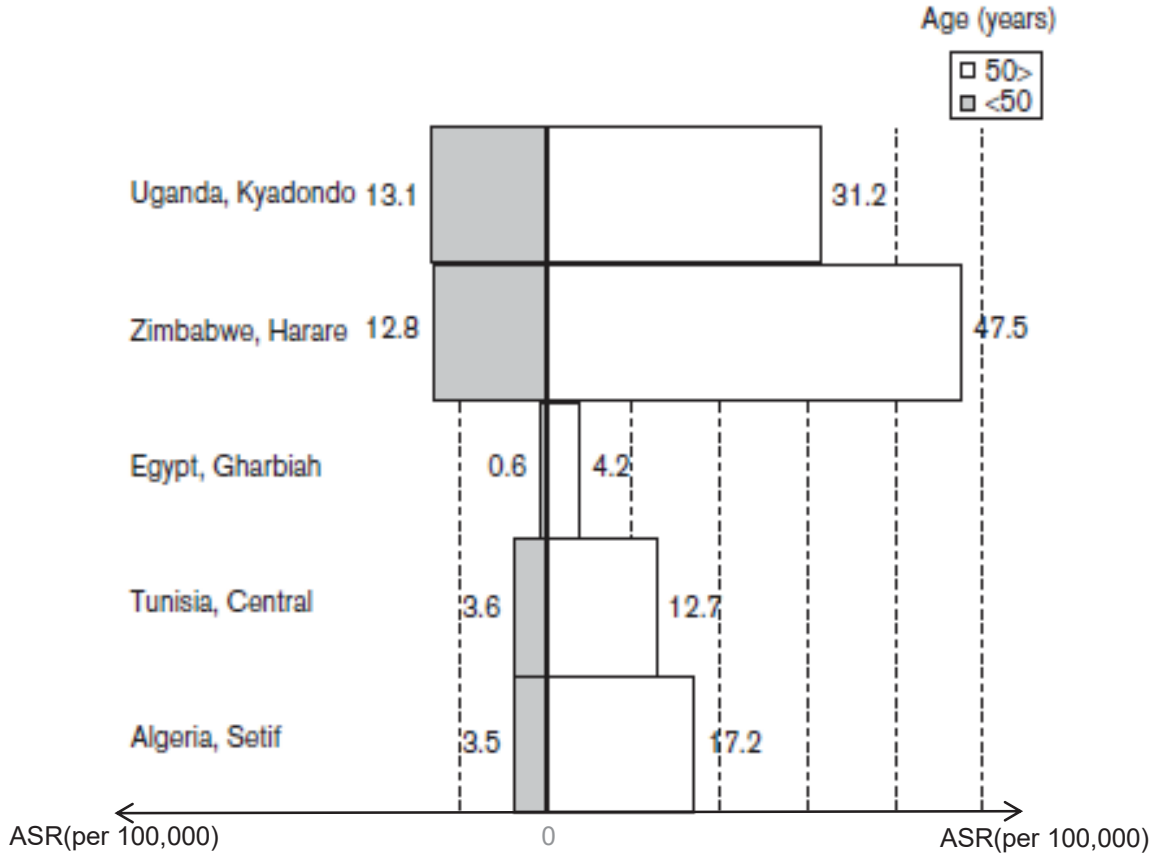


4.1.4.3 Cervical cancer

In each North African population, ASRs of cervical cancer were less than eight per 100,000, whereas in subSaharan African populations the ASR (African standard) was 4.5-fold higher (Harare: 32/100 000 and Kyadondo County: 34.8/100 000)(Figures ~~11 and~~ 12). Harare and Kyadondo County had similar age-specific incidence rates among the age groups below 50 years; however, in women aged above 50 years the incidence was

higher in Harare than in Kyadondo (Figure 15). Cervical cancer was the most common cancer in females in four of the five populations (the exception being Gharbiah) in this period.

Figure 14: Age-specific incidence (50y< and 50y>) of cervical cancer, 1998-2002 (per 100,000).



4.1.5 Discussion and conclusion

The magnitude of HIV prevalence varies worldwide and among African countries and regions as well. Arabic populations in North Africa (represented in this study by sites in Tunisia, Algeria, and Egypt) have low HIV/AIDS prevalence, estimated in 2001 as less than 0.2% (UNAIDS and WHO, 2010a). In Central Africa, HIV/AIDS prevalence in Uganda was between 6.1 and 6.5% for the period 1998–2002 (Parkin et al., 2010); Zimbabwe is one of the countries that is most affected by the AIDS epidemic in Africa (HIV prevalence: 33.7% in 2002) (UNAIDS and WHO, 2010a). Thus, in 2001 subSaharan Africa consisted of 28.5 million of the world's 40 million people living with HIV/AIDS (UNAIDS and WHO,

2008a). Despite Africa being the most-affected continent, the pattern of HIV prevalence is heterogeneous: lower HIV prevalence in the North African countries, intermediate prevalence in Uganda, and one of the highest prevalence in Zimbabwe (Figure 15).

In Zimbabwe, HIV prevalence in pregnant women attending antenatal clinics was reported to be 26% in 2002. HIV prevalence in people aged 15–29 years in the population-based Young Adult Survey, conducted in 2001–2002, was 21.8% and 10.3% among women and men, respectively (Mahomva et al., 2006). Estimated national adult (15–49 years) HIV prevalence was 18% in 2005–2006, 11% for young women (15–24 years), and 4% for young men [sex ratio (male:female): 0.36]. The prevalence of adults living with HIV was 21% for women and 15% for men [sex ratio (male:female): 0.71]. In Uganda, an estimated 6.7% of adults (15–49 years) were living with HIV in 2005. Infection levels were the highest among women [7.5% compared with 5.0% among men; sex ratio (male:female): 0.67 (UNAIDS and WHO, 2008b]. We assumed that during the study period, HIV prevalence in women was higher in Zimbabwe than in Uganda, this was consistent with the geographical pattern of HIV prevalence in the general population presented above, and thus HIV prevalence in women was higher than in men in Zimbabwe and Uganda in the period studied.

In Africa, access to ART was limited. In fact, in subSaharan Africa, the estimated ART coverage represented 100,000 people receiving treatment at the end of 2003 among 29.4 million people living with HIV/AIDS (0.3% of those living with HIV/AIDS). In all of North Africa and the Middle East the estimated number of people receiving ART was 1000 among 550,000 people living with HIV/AIDS (0.2% of people living with HIV/AIDS; WHO, 2010; UNAIDS and WHO, 2010a). An important factor was that all countries in these Arabic regions were experiencing concentrated and low-level epidemics. The population at risk for HIV infection in these regions are primarily intravenous drug users and sex workers, which means difficulties in reaching people who were HIV positive to treat them (WHO, 2010). Therefore, with respect to the low coverage of ART in Africa during the period studied, we assumed that our study was performed before the uptake of ART and its impact on the HIV epidemic, assuming that the patterns of AIDS-related cancers may not be influenced by ART.

4.1.5.1 Kaposi's sarcoma

Four clinicoepidemiological forms of KS have been described: (a) classic KS that occurs in elderly people of Mediterranean, Eastern European, and Middle Eastern heritage; (b) immunosuppressive KS observed in patients after solid organ transplantation, called iatrogenic or transplant-associated; (c) endemic African KS that occurs in people living in subSaharan Africa, presenting in four clinical variants (benign disease, aggressive form mainly localized to extremities, lymphadenopathic form, and visceral involvement form); and (d) epidemic AIDS-related KS (Sissolak and Mayaud, 2005). We observed, as expected, that KS is rare in general populations of North Africa. This may reflect the low prevalence of HIV/AIDS in this region. HHV-8 is considered to be the etiological agent of all clinic-epidemiological forms of KS [International Agency for Research on Cancer (IARC), 1997]; it is a necessary but insufficient cause of KS (Pfeiffer et al., 2010). Indeed, HHV-8 infection seems to be a very low risk factor for the development of KS. HHV-8 prevalence is high in some West African countries, such as Côte d'Ivoire and Gambia, whereas AIDS-related KS is rare in this region. Thus, the low incidence of KS in North African populations may not reflect a low prevalence of HHV-8.

~~Four clinico-epidemiological forms of KS have been described: (i) classic KS occurs in elderly people of Mediterranean, Eastern European, and Middle Eastern heritage; (ii) immunosuppressive KS observed in patients after solid organ transplantation, called iatrogenic or transplant-associated; (iii) endemic African KS occurs in people living in Sub-Saharan Africa and (iv) epidemic AIDS-related KS. So,~~ Endemic KS used to be the most common type of KS in subSaharan Africa; with AIDS emerging, however, the epidemic type became the most common (Sissolak and Mayaud, 2005). Indeed, between the 1950s and 1989–1991, KS incidence increased by more than 10-fold in men from Kyadondo County, reaching an ASR (African standard) of 30.3/100,000 (Wabinga et al., 1993) and remaining unchanged until 1998–2002. The increase of KS incidence observed between the 1950s and the end of the 1980s seems to reflect the emergence of the epidemic form of KS in Kyadondo County. In the HIV record-linkage study, implemented in Kyadondo County (Uganda), KS represented 54% of all cancers diagnosed among people living with HIV/AIDS between 1998 and 2002 (Mbulaiteye et al., 2006). The ASR (world standard) of

KS in Harare (Zimbabwe) and Kyadondo County (Uganda) in men and women was the highest in the world (Curado et al., 2008).

~~and~~ We also observed that the majority of KS cases occurred in the high-risk age group for HIV infection (15–49 years) in both sexes in 1998–2002. In the United States of America, before HAART was introduced, AIDS-associated KS occurred among younger age groups, as in Harare and Kyadondo. The peak of incidence occurred in the age group of 20–29 years in men who were nonhomosexual and at the age group of 30–39 years among men who were homosexual and bisexual. The age distributions of KS rates in men from both subSaharan populations studied seemed to be similar to that of people who were homosexual in the United States of America (Biggar et al., 1996).

Furthermore, we have observed that KS ASRs (Africa standard) in Harare and Kyadondo were higher in men than in women ~~[sex ratio (male:female): in Harare=1.9 : 1 and in Kyadondo=1.3 : 1~~; (p-values non significant for Kyadondo) although HIV prevalence was higher in women than in men (UNAIDS and WHO, 2008b). However, data show that in Uganda, men have higher prevalence of HHV-8 than women, which may explain the KS incidence gender distribution in both populations (Dollard et al., 2010). The predominance of men in KS was also observed in Tunisia (Ben et al., 2001) and in Sokoto (Nigeria) (Mbah et al., 2008), where epidemic form of KS incidence was low. This sex difference for KS in people with HIV/AIDS was also observed in Western countries (Armenian et al., 1993; Franceschi et al., 1995). ~~Furthermore,~~ In addition, although HIV prevalence in women from Zimbabwe was higher than in Ugandan women, we observed that the incidence of KS in Harare was similar to that in Kyadondo. ~~Data show that men have higher prevalence of HHV-8 than women, which may explain this difference. Indeed,~~ Ugandans have 2.33-fold greater odds of being HHV-8 infected than do Zimbabweans (Dollard et al., 2010). Despite most of the KS cases occurring in the high-risk age group for HIV infection, the described pattern of KS may not be similar to the distribution of HIV by sex or by population, suggesting that HHV-8 and other factors also contribute to the distribution of this malignant disease.

4.1.5.2 Non-Hodgkin lymphoma

NHL presents a wide range of subtypes of B-cell or T-cell lymphoma. The etiology of NHL is complex and can be associated with different viruses, including EBV [associated with

organ transplant, AIDS-related NHL, and Burkitt lymphoma (BL)], HHV-8 (primary effusion lymphoma), and human T-cell lymphotrophic virus type 1 (peripheral T-cell NHL). HIV seems to facilitate its development through its effects on the immune system (Bouvard et al., 2009), and requires coinfection with another virus. A newly identified link between HCV and NHL was reported (Bouvard et al., 2009). Relative risks were similarly increased for all major NHL subtypes (Marcucci and Mele, 2011). Although the mechanism of the interaction between the HIV and HCV is not completely known, HIV increases the progression of HCV (Singal and Anand, 2009; Jang et al., 2010).

During the study period, the HCV prevalence in Africa was the highest in the world (5.3% in 1999) (WHO 1999); Egypt has one of the highest rates of HCV, up to 20% (Darwish et al., 1996; Frank et al., 2000; El Gaafary et al., 2005). In Tunisia, the estimated HCV prevalence by the end of the 1990s was under 1.0% (Ben Nejma 1996; Triki et al., 1997; Kilani et al., 2007); in Algeria, it was around 1–3% in 2009 (Sari 2009). The overall prevalence of anti-HCV antibodies in subSaharan Africa was estimated to be approximately 3% (Uganda: 6.6%; Zimbabwe: 2.0%) (Madhava et al., 2002). We can classify the populations studied according to the HCV prevalence: low prevalence in Tunisia, Algeria, and Zimbabwe; intermediate prevalence in Uganda; and high prevalence in Egypt (Figure 3).

In Egypt, it has been demonstrated that HCV is a risk factor for diffuse large B cell, marginal zone, and follicular lymphomas (Cowgill et al., 2004). The HCV prevalence in patients with NHL is approximately 15% higher than among the general population (Gisbert et al., 2003). ~~The HCV prevalence in Egypt is one of the highest in the world, up to 20% (Darwish et al., 1996; Frank et al., 2000; El Gaafary et al., 2005), and NHL incidence in both sexes is also one of the highest in the world (Curado et al., 2008).~~ HCV infection in Egypt seems to be related to the parenteral antiSchistosomal therapy national campaigns held from the 1950s to the 1980s, which may have disseminated HCV in Egypt (Frank et al., 2000). HCV prevalence was the highest in the elderly population of the Lower Egypt region, where Gharbiah is situated (Cowgill et al., 2004), presenting a similar pattern of NHL incidence in Gharbiah by age (Figure 4); this governorate is an agricultural area where the parenteral antiSchistosomal therapy campaign was conducted [Middle East Cancer Consortium (MECC), 2010]. Compared with the other four regions in

Egypt (Cairo, Alexandria, Middle Egypt, and Upper Egypt), Lower Egypt presented the highest prevalence of antibodies to HCV between 1995 and 1996 (28.4%), whereas the overall prevalence was 21.9% (Frank et al., 2000). In addition, birth in rural areas and rice cultivation (possible markers for past exposure to HCV) were associated with diffuse large B-cell lymphoma (Ezzat et al., 2005); thus HCV infection may play a major role in the high NHL incidence in Gharbiah. The causative fraction of NHL attributable to HCV varies greatly by country, but is estimated to be around 10% in areas where HCV prevalence is high (Marcucci and Mele, 2011).

The EBV, endemic in tropical East Africa, Central Africa, and West Africa, has been associated with endemic BL (Burkitt and O'Conor, 1961). This may be one of the reason for the high incidence in the age group of 0–14 years observed in Kyadondo during this study period. The prevalence of BL among patients with NHL, between 1999 and 2004 at the Egyptian National Cancer Institute, a major referral center in Cairo, was 0.21%, this may mean that EBV did not contribute significantly to the high prevalence of NHL in the Gharbiah population. HIV may also have only a modest contribution to the overall incidence of NHL in Egypt because of the low prevalence of HIV/AIDS observed there. However, high HIV prevalence in Zimbabwe could explain the NHL incidence observed in Harare.

In subSaharan Africa there is a lower excess risk for NHL compared with the United States and Europe (Parkin et al., 2003). Indeed, relative risk of NHL among HIV-infected patients in the United States of America, before the advent of HAART, was more than 100-fold higher than in the general population (Goedert, 2000). In Kampala (Kyadondo County, Uganda), the risk of NHL in adults associated with HIV was lower than in high-resource countries, but for children BL is endemic (Parkin et al., 2000). NHL can be a relatively late manifestation of HIV infection (Beral et al., 1991), thus it is correlated with the duration of survival (Rabkin, 1994). Among HIV-positive hemophiliac patients, an average latency of 60 months has been reported before lymphoma diagnosis (Ragni et al., 1993). Furthermore, a history of KS is a risk factor for lymphoma emergence (Kalter et al., 1985). Since the introduction of HAART, which led to a dramatic decrease in KS, the relative proportion of NHL among all AIDS-defining illness may become larger (Matthews et al., 2000). This evidence may suggest, interalia, that the poor prognosis of African

AIDS patients (39% more deaths than would be expected in the absence of AIDS in Africa during 2001, UNAIDS and WHO, 2008a) due to the lack of access to ART may, at least in part, explain the lower risk for NHL observed in this region. Furthermore, before the introduction of HAART in the United States of America, the proportion of NHL as an AIDS-related illness was observed to be lower in the Black population (1%) than in the White population (3%); no specific genetic argument definitively supports the lower susceptibility of African HIV-positive populations to NHL (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1996). Finally, the low association between HIV and NHL in subSaharan countries compared with developed countries might also be partly due to the underascertainment of NHL incident cases that can occur in middle-income and low-income countries (Sasco et al., 2010).

4.1.5.3 Cervical cancer

One of the main causes of cervical cancer is HPV. The oncogenic HPV types found most frequently in cervical cancer are HPV 16, 18, 31, 33, 35, 45, 52, and 58 (Bouvard et al., 2009). The prevalence of HPV among women with normal cytology (no abnormal cells observed on the surface of the cervix upon cytology) in Northern Africa was 10.9% (Algeria: 10.5%, Tunisia: 14.6%, and Egypt: 10.3%) and 33.6% in East Africa (Zimbabwe: 24.7%; Uganda: no data available) [WHO and ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre), 2010]. The most prevalent HPV types found among 5872 African women with normal cytological finding in Africa were oncogenic types: 16, 52, 31, 35, 18, 45, and 58 (prevalence of 3.5%, 2.4%, 1.8%, 1.8%, 1.8%, 1.7%, and 1.6%, respectively) (Bruni et al., 2010).

SubSaharan populations were more infected by HPV than North African populations, this may explain the geographical pattern of cervical cancer observed in Africa (Figure 2). The difference in HIV prevalence, reproductive behavior factors, hormonal contraceptive use, and smoking may also contribute to the geographical distribution of cervical cancer (Maucort-Boulch et al., 2008).

In Kampala (Kyadondo County, Uganda) the prevalence of HPV infection among women aged between 12 and 24 years, presenting for health services in 2002–2004, was 74.6%, and HIV prevalence was 8.6% (Banura et al., 2008). This high HPV prevalence is indeed generally observed between the ages of 16 and 20 years [World Health Organization

(WHO), United Nations Population Fund, 2010]. However, there is a long latency period between primary infection with HPV and cancer emergence (Mougin et al., 2001); and the substantial correlation between the high-risk HPV population prevalence and cervical cancer incidence is observed among middle-aged and elderly women (Maucort-Boulch et al., 2008). We observed that Harare and Kyadondo County had similar age-specific incidence rates in the high-risk age group for HIV/AIDS (aged: 15–49 years) (Figure 6); however, in women aged above 50 years, the incidence of cervical cancer was higher in Harare than in Kyadondo. This observation may suggest a higher prevalence of an oncogenic subtype of HPV or early sexual activity~~, or higher smoking prevalence~~ in women from Harare in addition to the contribution of the high prevalence of HIV infection.

Tabacco use in these both populations has been observed in <1% of Zimbabwean and Ugandan women aged between 15 and 49 years (Pampel, 2008); thus tobacco may not had an important impact on cervical cancer emergence. Oral contraception has been more used in North African populations studied than these both subSaharan African populations (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1999) and (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007); this may be a co-factor explaining cervical cancer incidence in North African populations.

In developed countries, the wide coverage of cytology-based screening programmes reduces the incidence of invasive cervical cancer by allowing early detection and treatment of precancerous lesions. However, screening programmes were nonexistent in Uganda and Egypt in the period studied (Curado et al., 2008), and the estimated coverage of cervical cancer screening in 2001–2002 was low in the other populations studied, around 7% in Zimbabwe and Tunisia (Algeria: no data available) [WHO and ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre), 2010]. Therefore, the potential confounding effect of screening on cervical cancer incidence due to similar incidence rates at young ages may be insignificant in the study of these populations.

4.1.5.4 Data quality

Cancer data quality is limited in these five African registries. Indeed, despite indicating a good data validity, the near-100% fraction of MV cancers observed in North African

registries gives rise to suspicion of incompleteness (Parkin et al., 1996). In Harare and in Kyadondo County, the percentage of MV is less compared with that expected in Africa (Parkin et al., 2003); this is a potential indicator of poor data validity in these cancer registries. In addition, the percentage of DCO observed in Harare shows that there were a number of cancer cases with no information on the methods used to diagnose them, this also indicates poor data validity (Abu-Raddad et al., 2010a). Furthermore, HIV data quality is limited in North Africa; indeed, data are not collected from the populations where HIV continues to spread (female sex workers, intravenous drug users, and men who have sex with men). However, there is no evidence for an HIV epidemic in the general population in Algeria, Tunisia, or Egypt (Abu-Raddad et al., 2010b). In Africa, generally speaking, reported HIV cases come from surveillance systems of varying quality (UNAIDS and WHO, 2010b). Although the five population-based cancer registries cover only a small part of the population on the African continent (0.7%), and HIV and cancer data quality is limited, this information can contribute to enhancing and promoting cancer control.

For NHL, Gharbiah presented significantly highest incidences in both sexes. KS incidence was significantly higher in men than in women in subSaharan Africa, but the rates were similar for women in Harare and in Kyadondo. HIV prevalence in Harare was higher than in Kyadondo in the studied period. Cervical cancer incidence rates were higher in Harare than in Kyadondo in women aged above 50 years, and the combined subSaharan population rate (all ages) was 4.5-fold higher than that of the combined North African populations.

In conclusion, despite Africa being home to the regions most and the least affected by the AIDS epidemic, the distribution of these three AIDS-related cancers did not follow patterns of HIV prevalence in this study period. Although HIV infection increases the incidence of these cancers, cofactors such as infections and perhaps other factors may also contribute to the specific geographical patterns and age distribution of KS, NHL, and cervical cancer in Africa.

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4.1.8 Appendix

The following results (Table 4 and 5) completes those presented in the article titled “Geographical pattern of KS, NHL and cervical cancer associated with HIV infection in five African populations”. Fisher Exact’s tests were performed to assess whether the differences in incidence between populations and between genders were significant or not. The p-value threshold of α is 0.05.

Table 4: Geographical pattern of the ASR (per 100,000) of KS, NHL and cervical cancer in five African populations, 1998–2002

a- Kaposi sarcoma

sex	Population	Cases	PY	CR	ASR(A)	CIF	95% CI	p-value
Male	Algeria, Setif	1	3,423,181	0.0	0.0	2072.1	291.7 ; 14719.0	<0.001*
	Egypt, Gharbiah	9	7,430,472	0.1	0.1	457.1	234.9 ; 889.4	<0.001*
	Tunisia, Central	4	1,252,500	0.3	0.2	250.2	92.0 ; 680.8	<0.001*
	Zimbabwe, Harare	1734	4,339,135	40.0	50.4	Ref		
	Uganda, Kyadondo	768	3,670,075	20.9	30.2	1.7	1.5;1.8	<0.001*
Female	Algeria, Setif	1	3,404,260	0.0	0.0	1790.6	252.1 ; 12719.8	<0.001*
	Egypt, Gharbiah	1	7,231,625	0.0	0.0	6592.1	928.0 ; 46827.6	<0.001*
	Tunisia, Central	5	1,221,500	0.4	0.3	187.9	74.9 ; 471.2	<0.001*
	Zimbabwe, Harare	880	4,344,909	20.3	26.3	Ref		
	Uganda, Kyadondo	615	3,964,753	15.5	23.6	1.1	1.0;1.2	0.20

b- Non-Hodgkin lymphoma

sex	Population	Cases	PY	CR	ASR(A)	CIF	95% CI	p-value
Male	Algeria, Setif	130	3,423,181	3.8	3.8	3.1	2.6 ; 3.7	<0.001*
	Egypt, Gharbiah	869	7,430,472	11.7	11.9	Ref		
	Tunisia, Central	71	1,252,500	5.7	5.3	2.2	1.7 ; 2.9	<0.001*
	Zimbabwe, Harare	245	4,339,135	5.6	7.3	1.6	1.4 ; 1.9	<0.010
	Uganda, Kyadondo	147	3,670,075	4.0	4.8	2.5	2.0 ; 3.0	<0.001*
Female	Algeria, Setif	96	3,404,260	2.8	2.7	2.6	2.1 ; 3.2	<0.001*
	Egypt, Gharbiah	548	7,231,625	7.6	7.0	Ref		
	Tunisia, Central	38	1,221,500	3.1	2.4	2.9	2.1 ; 4.2	<0.001*
	Zimbabwe, Harare	187	4,344,909	4.3	5.7	1.2	1.0 ; 1.5	0.011*
	Uganda, Kyadondo	125	3,964,753	3.2	3.9	1.8	1.4 ; 2.2	<0.001*

c- Cervical cancer

Population	Cases	PY	CR	ASR(A)	CIF	95% CI	p-value
Algeria, Setif	229	3,423,181	6.7	7.6	4.2	3.4 ; 5.2	<0.001
Egypt, Gharbiah	109	7,430,472	1.5	1.3	24.6	19.1 ; 31.6	<0.001
Tunisia, Central	72	1,252,500	5.7	5.1	6.3	5.6 ; 6.9	<0.001
Zimbabwe, Harare	809	4,339,135	18.6	32.0	Ref		
Uganda, Kyadondo	643	3,670,075	17.5	34.8	0.9	0.8 ; 1.0	0.58

PY: persons-years; CR: crude rate; ASR(A): incidence rate standardized by age with African standard population; CIF: comparative incidence figure; Ref: reference; 95% CI: 95% confidence interval

Table 5: Gender comparisons of KS and NHL in the five African populations studied, 1998-2002

a- Kaposi sarcoma

Population	sex	Cases	PY	CR	ASR(A)	CIF	95% CI	p-value
Zimbabwe, Harare	Male	1734	4,339,135	40.0	50.4	1.9	1.7 ; 2.1	0.03
	Female	880	4,344,909	20.3	26.3			
Uganda, Kyadondo	Male	768	3,670,075	20.9	30.2	1.3	1.1 ; 1.4	0.95
	Female	615	3,964,753	15.5	23.6			

b- Non-Hodgkin lymphoma

Population	sex	Cases	PY	CR	ASR(A)	CIF	95% CI	p-value
Algeria, Setif	Male	130	3,423,181	3.8	3.8	1.4	0.5 ; 0.9	0.13
	Female	96	3,404,260	2.8	2.7			
Egypt, Gharbiah	Male	869	7,430,472	11.7	11.9	1.7	1.5 ; 1.9	0.40
	Female	548	7,231,625	7.6	7.0			
Tunisia, Central	Male	71	1,252,500	5.7	5.3	2.2	1.5 ; 3.4	0.91
	Female	38	1,221,500	3.1	2.4			
Zimbabwe, Harare	Male	245	4,339,135	5.6	7.3	1.3	1.1 ; 1.6	0.51
	Female	187	4,344,909	4.3	5.7			
Uganda, Kyadondo	Male	147	3,670,075	4.0	4.8	1.2	0.9 ; 1.6	0.75
	Female	125	3,964,753	3.2	3.9			

PY: persons-years; CR: crude rate; ASR(A): incidence rate standardized by age with African standard population; CIF: comparative incidence figure; Ref: reference; 95% CI: 95% confidence interval

Transition

In the first article (Section 4.1), I described the geographical patterns of three AIDS-related cancers in three northern African and two sub-Saharan African populations. The following paper describes trends in Kaposi sarcoma incidence over four decades in relation to HIV/AIDS prevalence in the two sub-Saharan African countries of Uganda and Zimbabwe. Successes of prevention programmes and a scale-up of antiretroviral therapy coverage have resulted in control of the HIV/AIDS epidemic and an observed decline in HIV/AIDS prevalence. This study aimed to describe how these changes in the HIV/AIDS epidemic have impacted the temporal and geographical patterns of the incidence of the most common AIDS-related cancer, Kaposi sarcoma.

4.2 Kaposi sarcoma trends in Uganda and Zimbabwe: a sustained decline in incidence?

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4.2.1 Abstract

Trends in Kaposi sarcoma (KS) incidence over four decades were described for Zimbabwe and Uganda. KS data were retrieved from the population-based cancer registries of Bulawayo (1963–71) and Harare (1990–2005), Zimbabwe, and Kyadondo, Uganda (1960–71 and 1991–2007). Joinpoint regression models were used to analyze time trends of KS incidence. Trends were compared to HIV/AIDS trends and were also described as rates versus birth cohort by age. In both countries, an increased incidence of KS accompanied the emergence of the HIV/AIDS epidemic (p-value<0.0001). In Zimbabwe, KS incidence (both sexes, all ages) changed in parallel to that of HIV/AIDS prevalence, whereas in Uganda, despite an observed decrease in HIV/AIDS prevalence since 1992, we observed a decrease in KS incidence in men younger than 50 years (Annual Percent Change, APC after 1991=-4.5 [-5.6; -3.4] , p-value<0.05) but not in men aged>50 years (APC after 1991=1.0 [-2.8; 5.0]) nor in women (APC=1.0 [-0.6; 2.6]). In both populations, a period effect at older ages was observed, with initial increases in incidence in men followed subsequently by a downturn in rates of the same magnitude. The uniformly declining rates in younger men (aged under 30 years) suggested that a recent cohort effect was also in operation with a reduced risk in generations born after the mid-1950s in Uganda and in the mid-1960s in Zimbabwe. The combined introduction of antiretroviral therapy and effective prevention programmes against HIV/AIDS appeared to be the key contributors to the KS decline observed in both Uganda and Zimbabwe.

4.2.2 Introduction

Kaposi sarcoma (KS) has been a common form of cancer among indigenous populations in Sub-Saharan Africa for many decades (Taylor et al., 1971). Prior to the HIV/AIDS epidemic (in the 1970s), KS accounted for around 9% of all histologically-confirmed malignant tumours in central African region and 3% in Zimbabwe (THIJS, 1957). By 1990, the incidence rates of KS had increased 20-fold to 55 per 1000 in Uganda (Kyadondo County) and to 22 per 1000 in Zimbabwe (Harare) (Cook-Mozaffari et al., 1998). HIV infection and AIDS has been shown to greatly increase the risk of Kaposi Sarcoma. A study in the USA showed that 81% of KS cases occurred in people living with HIV/AIDS (Shiels et al., 2011). Despite the reduced risk of KS after the introduction of antiretroviral therapy (ART) in the mid-1990s in the USA, the rate of KS was still 140 times higher among men with HIV/AIDS compared to those without HIV infection (Seaberg et al., 2010). The decline in HIV infection in Zimbabwe and Uganda has been attributed to HIV/AIDS prevention programmes including prevention of mother-to-child and sexual transmission, as well as to uptake of ART(Green et al., 2006),(Halperin et al., 2011). A European study assessing the KS risk before and after implementation of ART for example, reported a 11-fold reduction in risk of KS (Franceschi et al., 2010). In Africa, primary prevention is a central strategy in HIV/AIDS control. Generally, the ART coverage in sub-Saharan Africa is lower compared with developed countries, but the recent uptake has been dramatic i.e. among the 4.7 million people in need of antiretroviral therapy in Sub-Saharan Africa, 100,000 people received treatment at the end of 2003 (ART coverage=2%) as compared with 310,000 at the end of 2004, and 810,000 at the end of 2005 (ART coverage=17%) (WHO, 2006).

This paper aims to describe the changes in KS incidence before and subsequent to the HIV/AIDS epidemic in Zimbabwe and Uganda using the best available population-based cancer registry data available data from Zimbabwe and Uganda. Changes over time in the incidence of KS were analysed alongside concomitant trends in HIV/AIDS prevalence. Additionally, sex-specific differences in KS incidence were examined and an assessment made of whether the reported male predominance of KS before the HIV/AIDS epidemic (Sanders, 1997) (Parkin et al., 1999) (Cook-Mozaffari et al., 1998) prevails.

4.2.3 Material and Methods

4.2.3.1 Data sources

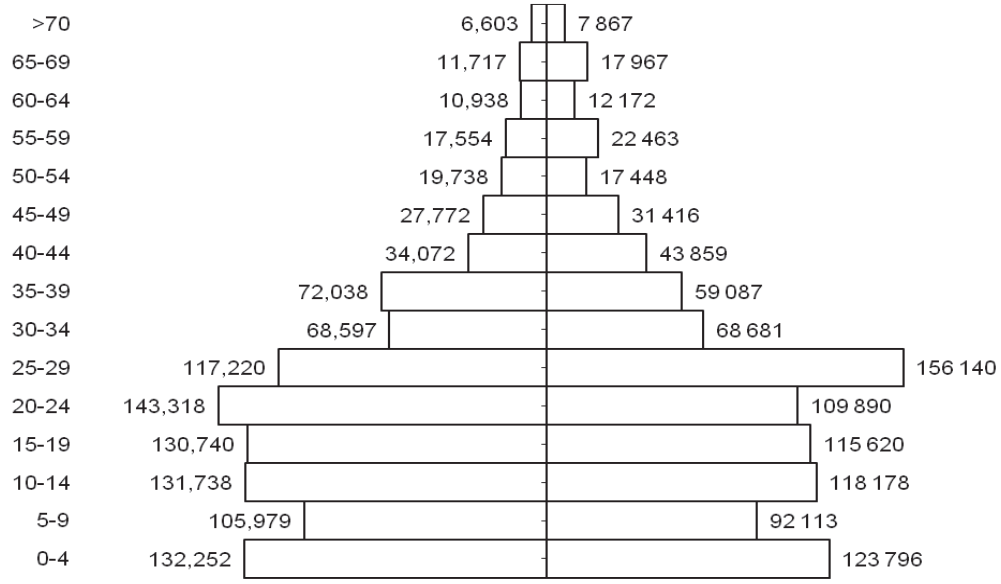
HIV/AIDS prevalence data among adults aged 15-49 by calendar year (1990-2007) and country were obtained from United Nation AIDS (UNAIDS and WHO, 2010). As for KS (ICDO=C46 (Fritz et al., 2000)) incidence, data were taken from population-based cancer registries in two Sub-Saharan African countries: Kampala, 1960-71 and 1991-2007 (Uganda), Bulawayo, 1963-71 and Harare, 1990-2005 (Zimbabwe).

The Bulawayo Cancer Registry in Zimbabwe was founded in 1963 and functioned for 15 years until 1978. It covered the south-western part of Zimbabwe with a population of around 160,000 circa 1969 (Parkin et al., 1994). The national Cancer Registry in Harare was established in 1985 to register cancers in Zimbabwe. It is located in the north-eastern part of the country covering a population of 2.02 million in 2005 (17.4% of the total population) (Chokunonga et al., 2000) (Figure 16.a). Kyadondo Cancer Registry (KCR) is a population-based cancer registry in Uganda covering a population of 1.6 million people in 2007 (6.6% of the total population) (Figure 16.b). The area covered by KCR comprises of Kampala, the capital city, and part of Wakiso district. KCR was established in 1951 but stopped functioning between 1971 and 1990 because of instability in the country. It resumed activities in 1991 (Wabinga et al., 2010).

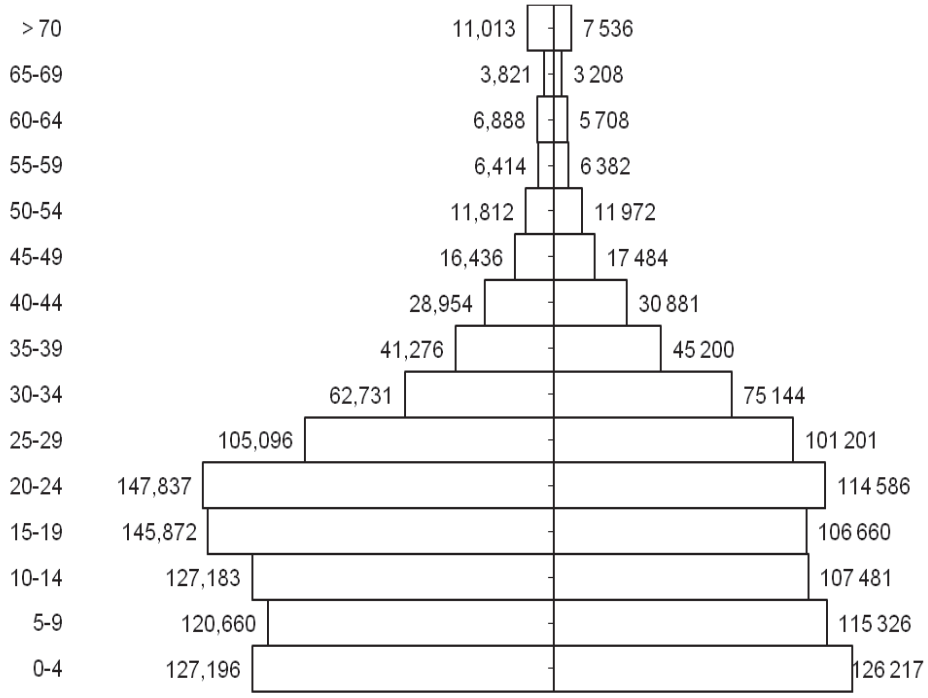
Data from these registries appeared in successive Volumes of Cancer Incidence in Five Continents (CI5) published by IARC (2012), for which specific quality criteria must be met, e.g. for the volume IX, a proportion of tumors which were morphologically verified (%MV) more than 60% but less than 99-100% and a percentage of cases identified as registered from death certificates only (%DCO) less than 20% (Curado MP et al., 2008).

Figure 15: Average annual population at risk in (a) Zimbabwe (Harare, 2001-05) and (b) Uganda (Kyadondo, 2001-07)

a- Zimbabwe (Harare, 2001-2005)



b- Uganda (Kyadondo, 2001-07)



Women on the left side and men on the right side.

Note: This figure is not presented in the article published in the International Journal of Cancer

4.2.3.2 Statistical Analysis

Age-specific incidence rates (ASI) were estimated for the 4 age groups 0-19, 20-39, 40-59 and ≥60 in both genders from Zimbabwe (Bulawayo in 1963-72 and Harare in 1991-2002) and Uganda (Kyadondo in 1960-71 and 1991-2002). Furthermore, age standardized incidence rates (ASR) were estimated using direct standardization with the African standard population (Dos Santos Silva, 1999) given its similar age structure to the populations studied and the high burden at younger ages. These rates were expressed as rates per 100,000 persons. Comparison between pre- and during AIDS epidemic (1991-2002) periods; and between genders and populations during AIDS epidemic (1991-2005) were performed using chi-square and Fisher exact's tests. Šidàk correction was used to counteract the problem of multiple comparisons and control the family-wise error rate because individual tests were assumed to be independent (Šidàk, 1967). Instead of using a p-value threshold of α=0.05, a stricter threshold with was used $\beta = 1 - (1 - \alpha)^{1/n}$. Here, n represents the number of individual tests performed and β was equal to 0.004.

Rates were compared and expressed as standardized rate ratios (SRR). We calculated 95% confidence intervals (95%CI) for the SRR based on the Poisson distribution. SRRs were considered statistically significant when the 95%CI did not include unity.

KS annual ASR (overall and truncated in two age categories: <50 and ≥50 years old) were computed by sex and population. A log-linear regression model with age-adjusted rates as the response was used to determine joinpoints in the trends of KS incidence. Standard errors of rates were included in the analysis to take into account the uncertainty stemming from different denominators for those rates. These are breakpoints in time for which significant changes in the linear trends are detected. They enable estimation of the magnitude of the trend – the Annual Percent Change (APC) between each linear segment defined between two joinpoints. A maximum number of four joinpoints was specified (Statistical Research and Applications Branch, 2008). To quantify the trend for two fixed predetermined time periods, we estimated the Average Annual Percent Change (AAPC), based on a method that uses the underlying Joinpoint model to compute a summary measure over the pre-specified intervals. It is computed as a weighted average of the APC's from the Joinpoint model, with the weights equal to the length of the APC interval (Clegg et al., 2009). Joinpoint analyses were performed using the 'Joinpoint' software

from the Surveillance Research Program of the US National Cancer Institute (Statistical Methodology and Applications Branch and Data Modeling Branch, 2011).

To examine the KS incidence trends according to generation (cohort), ten-year synthetic birth cohorts were obtained by subtracting the midpoints of the 5-year age groups from the corresponding midpoints of 5-year calendar time. The trends are presented as rates versus birth cohort by age (in 5-year age groups).

4.2.4 Results

Prior to the HIV/AIDS epidemic (during the 1960s), age-specific rates of KS ranged between close to 0 to 8/100,000 in Zimbabwe and Uganda (Table 5). During the emergence of HIV/AIDS, the highest rates of KS in males was observed for the 40-59 years age group with a 20- and 10-fold increase in risk of KS compared with the pre-HIV/AIDS era in Zimbabwe and Uganda respectively. A higher overall increase of KS among males in Zimbabwe (SRRpre/post=29.2, p-value<0.0001) resulted in a 30% higher rate of KS in Zimbabwe during the HIV/AIDS epidemic period as compared to Uganda (SRRZimbabwe/Uganda=1.3, p-value<0.0001).

There were 4237 KS cases in men and 1860 in women in Harare, Zimbabwe (1990-2005); and 2750 in men and 2020 in women in Kyadondo, Uganda (1991-2007). A male predominance was observed in both countries with a lower magnitude during AIDS-epidemic (e.g. SRRM/F=17.1, p-value=0.002 in Uganda in the pre-HIV/AIDS epidemic period versus 1.5, p-value<0.0001 during the HIV/AIDS epidemic period) (Table 6). Reduced gender difference was partly a result of a higher overall increase in rates in females as compared to males (SSRpre/during=72.4, p-value<0.0001 in females in Zimbabwe and SSRpre/during=126.5, p-value<0.0001 in Uganda).

Table 6: Age-specific and age standardized rates of Kaposi sarcoma incidence before (1960-72) and during AIDS epidemic (1991-2002) according to sex in Uganda and Zimbabwe

			Pre-AIDS epidemic				During AIDS-epidemic				SRRpost/pre	*p-value**
Sex	Population	Age groups	cases	PY	ASI	ASR	cases	PY	ASI	ASR	(95%CI)	
Male	Zimbabwe[1]	0-19	1	39,584	0.3	1.7	89	3,873,668	2.3	48.4	29.2 (16.0-53.4)	<0.0001
		20-39	6	46,831	1.3		2,23	3,644,540	61.2			
		40-59	8	17,911	4.5		1,092	1,113,475	98.1			
		>60	1	1,304	7.7		150	215,631	69.6			
	Uganda[2]	0-19	4	93,722	0.4	2.9	210	3,985,151	5,3	34.4	11.7 (8.9-15.5)	<0.0001
		20-39	26	92,251	2.8		1,191	2,965,317	40,2			
		40-59	18	24,332	7.4		450	612,884	73.4			
		>60	6	78,156	7.7		68	151,93	44.8			
Female	Zimbabwe[1]	0-19	1	37,986	0.3	0.3	56	4,287,737	1.3	22.7	72.4 (23.0-227.6)	<0.0001
		20-39	2	28,562	0.7		1,093	3,354,808	32.6			
		40-59	0	6,227	0.0		326	762,186	42.8			
		>60	0	562	0.0		25	132,592	18.9			
	Uganda[2]	0-19	2	91,753	0.2	0.2	149	4,149,239	3.6	21.7	126.5 (40.5-395.8)	<0.0001
		20-39	1	59,437	0.2		850	2,563,717	33.2			
		40-59	0	1,587	0.0		147	470,438	31.2			
		>60	0	67,404	0.0		19	183,102	10.4			

[1] pre-AIDS epidemic (1963-72) in Bulawayo
during AIDS-epidemic (1991-2002) in Harare

[2] pre-AIDS epidemic (1960-71) in Kyadondo
during AIDS-epidemic (1991-2002) in Kyadondo

PY: person-year at risk for Kaposi sarcoma

ASI: age-specific incidence rate (per 100,000)

ASR: age standardized incidence rate (per 100,000 African standard population)

95%CI: 95% confidence interval

* : Fisher exact's comparing cases pre- and during AIDS epidemic, according to Sidak correction (β=0.004)

Table 7: Comparisons of age standardized rates (ASR) of Kaposi sarcoma incidence according to sex and studied population in 1991-2005

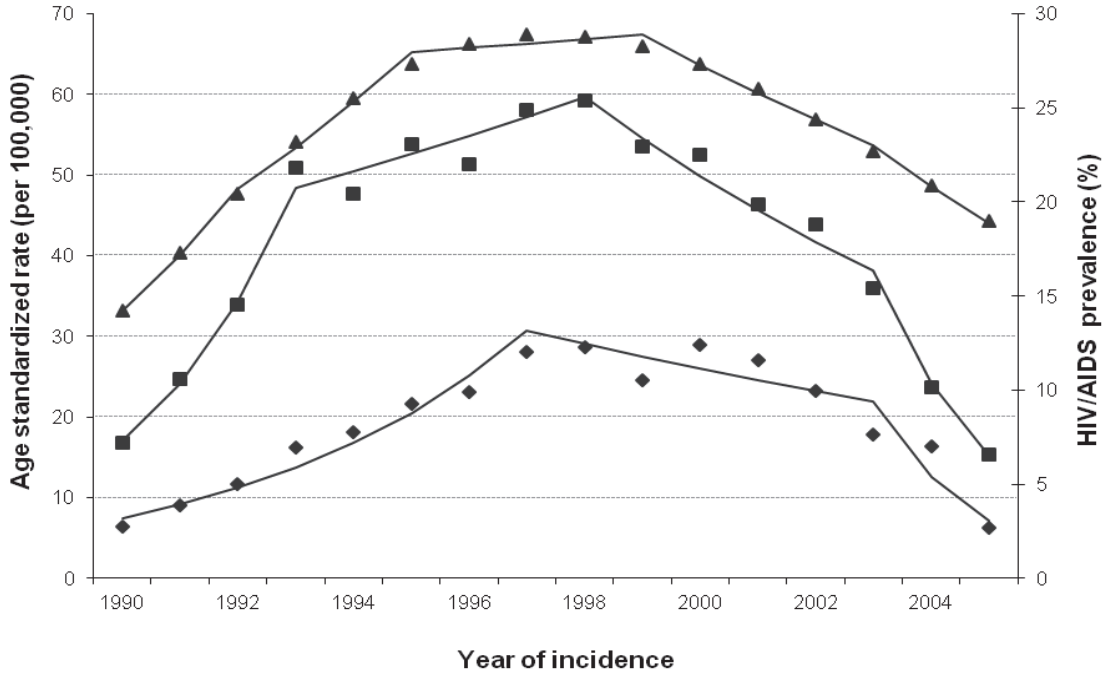
			Males vs Females			Zimbabwe vs Uganda[1] in Males			Zimbabwe vs Uganda[1] in Females		
Population	Sex	ASR	SRR	95%CI	*p-value*	SRR	95%CI	*p-value*	SRR	95%CI	*p-value*
Zimbabwe (Harare)	Males	42.5	2.1	2.0-2.2	<0.0001	1.3	1.2-1.4	<0.0001	0.9	0.85-0.98	<0.0001
	Females	20.1									
Uganda (Kyadondo)	Males	32.5	1.5	1.4-1.6	<0.0001						
	Females	22.1									

[1]: Zimbabwe versus Uganda between 1991 and 2005
ASR: age standardized incidence (per 100,000 African standard population)
SRR: standardized rate ratio
95%CI: 95% confidence interval

The time trends in KS rates in Zimbabwe followed almost exactly the pattern of HIV/AIDS prevalence (Figure 16.a). Between 1990 and 1998, the ASR for KS increased from 17 to 60 per 100,000 for males and from 8 to 31 per 100,000 for females. Annually among males a 41.2% (95%CI=23.6; 61.2) and 4% (95%CI=-0.3; 9.5) increase in rate in 1990-1993 and in 1993-1998 respectively was observed. For females, the annual increase in rate between 1990 and 2001 was 8.9% (95%CI=3.0; 15.1). After 1998 in males (-8.5%, 95%CI=-12.2; -4.8 in 1998-2003; and -37.0%, 95%CI=-47.4; 24.6 in 2003-2005) and after 2001 in females (-26.1%, 95%CI=-37.8; -12.3), rates steadily decreased in both sexes and reached the rates observed in 1990 by 2005. The joinpoint analysis further supported this observation (Table 7). In Zimbabwe the trend of KS differed to that observed in Uganda in two ways. Firstly, the trend in KS followed that of HIV/AIDS prevalence for both sexes in Zimbabwe. On the other hand, only male KS rates followed the HIV/AIDS prevalence in Uganda (-3.2%, 95%CI=-4.4; -1.9] between 1990 and 2007), whereas the female rates for KS showed a relatively stable trend over the study period (Figure 17.b). Secondly the timing of the change in incidence and prevalence differed: HIV/AIDS prevalence and KS incidence rates among males in Zimbabwe were decreasing only after 1998; in Uganda the decrease was seen since the early 90s. Age-specific trends in KS rates according to age groups (categorised into two groups below and over 50 years) and sex were also examined (results not shown). Incidence rates in both sexes in Zimbabwe decreased only during the early 2000s for both age groups. In Uganda, decrease in KS rate was observed during the whole period (between 1991 and 2007) in men younger than 50 years (AAPC= -4.5%, 95%CI=-5.6; -3.6]) but remained constant over time in men older than 50 years and in women.

Figure 16: Age standardised rates of Kaposi Sarcoma incidence and national HIV/AIDS prevalence among (15-49 years old) adults, in (a) Zimbabwe (Harare, 1990-2005) and in (b) Uganda (Kyadondo, 1991-2007)

a- Zimbabwe



b- Uganda

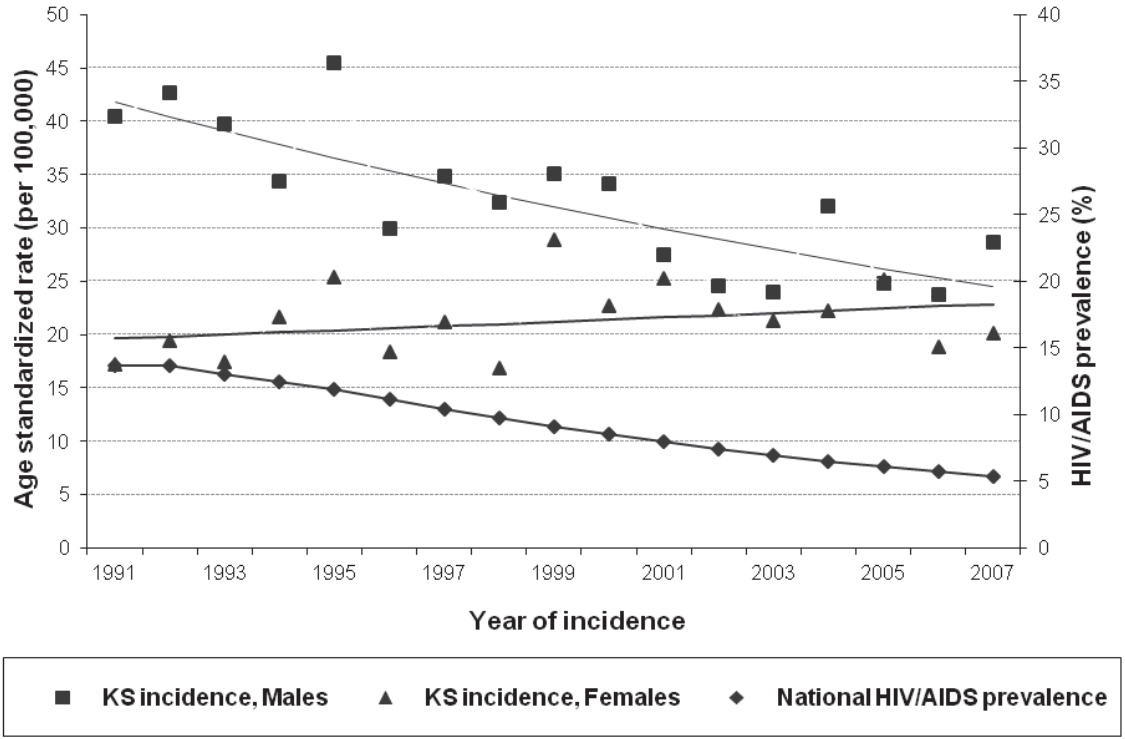


Table 8: Trend of Kaposi sarcoma incidence in Zimbabwe (Harare, 1990-2005) and Uganda (Kyadondo, 1991-2007) according to sex

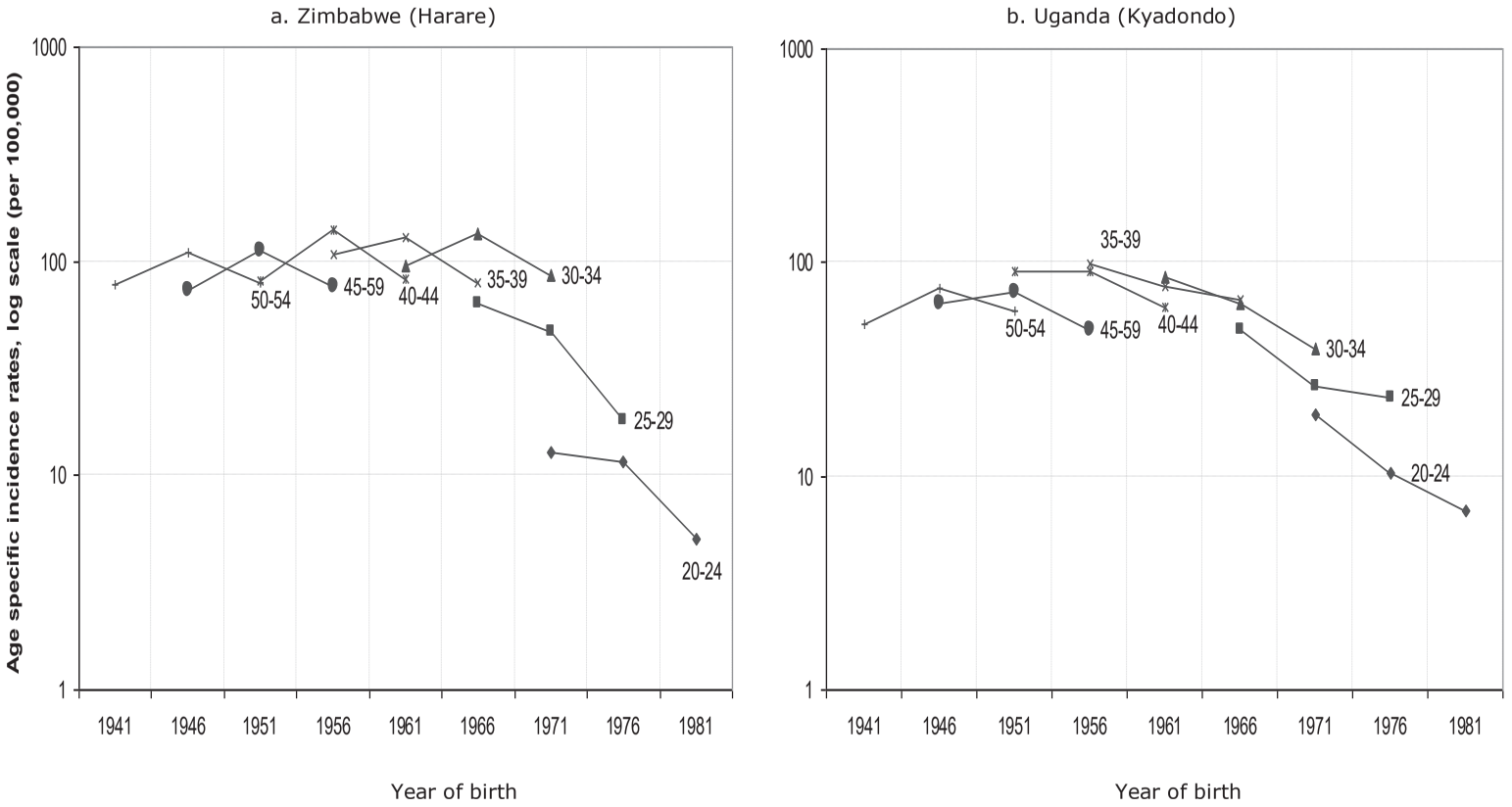
	Full Range		Trend 1		Trend 2	
	Years	AAPC (95%CI)	Years	AAPC (95%CI)	Years	AAPC (95%CI)
Zimbabwe						
KS incidence in males	1990-2005	-0.8 (-3.9;2.4)	1990-1998	16.9* (11.9;22.2)	1999-2005	-19.2* (-23.2;-15.1)
KS incidence in females	1990-2005	-1.8 (-7.0;3.7)	1990-1998	8.9* (3.0;15.1)	1999-2005	-15.9* (-24.2;6.8)
Uganda						
KS incidence in males	1991-2007	-3.2* (-4.4;-1.9)	1990-1998	-3.2* (-4.4;-1.9)	1999-2007	-3.2* (-4.4;-1.9)
KS incidence in females	1991-2007	0.3 (-1.4;2.0)	1990-1998	0.3 (-1.4;2.0)	1999-2007	0.3 (-1.4;2.0)

*: significantly different from zero (P<0.05)

AAPC: average annual percent change

Figure 17 shows the KS incidence trends by 5-year age groups plotted against birth cohort in Zimbabwe (Figure 17.a) and Uganda (Figure 17.b). Both populations presented similar but shifted trends. A period effect was observed in older age groups with initial increases in KS incidence followed subsequently by a downturn of same magnitude in men aged 30 years and older in Zimbabwe and aged 40 years and older in Uganda. However, for men aged less than 29 years in Zimbabwe and aged less than 39 years in Uganda, rates uniformly decreased. This difference in trends between generations suggested a cohort effect was also in operation with a reduced risk for KS in generations born after the mid-1950s. The curves for older men appeared to turn downward near 1960s in Zimbabwe and near 1950s in Uganda.

Figure 17: Age-specific rates of Kaposi Sarcoma incidence according to time at birth in male in (a) Zimbabwe (Harare) and (b) Uganda (Kyadondo)



4.2.5 Discussion

In this study, we reported marked changes in KS incidence in two African populations during the last 4 decades. A strengthening of the decrease in KS rates was observed during the most recent time period. It is likely that the decline in the incidence of KS during the 1990s was related to the decrease in HIV/AIDS prevalence. The decline in KS incidence was mostly evident for males in both populations and females in Zimbabwe, whereas the rates for females were stable over the last two decades in Uganda.

KS was relatively common in sub-Saharan Africa before the HIV/AIDS epidemic (Thijs, 1957) and this “endemic” form of KS was recognized since the 1950s as a common neoplasm in native populations of Sub-Saharan Africa (Sissolak and Mayaud, 2005). During this period, we found KS incidence was higher in Uganda than in Zimbabwe. Furthermore, consistent with a previous report (Cook-Mozaffari et al., 1998), we found a male predominance. After the emergence of the HIV/AIDS epidemic in the 1990s, we observed an increased incidence of KS in all age groups with an incidence peak at age 40-59 years that was consistent with the “epidemic” form of KS, which generally affects younger age groups (Sissolak and Mayaud, 2005).

The first HIV/AIDS epidemic was reported in Kinshasa (Democratic Republic of Congo) in the 1970s. It reached epidemic levels in the Eastern African region (including Uganda) in the early 1980s (Serwadda et al., 1985) (Okware, 1987), and only afterwards in Southern Africa (including Zimbabwe). By the end of the 1980s, Zimbabwe and other southern African countries such as Malawi, Zambia and Botswana overtook East Africa as the focus of the HIV/AIDS epidemic (Hiza, 2010). We found a decrease in the KS incidence in Uganda occurring in the 1990s, followed subsequently by Zimbabwe (from around 2000). This marked decline in KS incidence was most likely caused by a combination of several changes surrounding the HIV/AIDS epidemic.

The decline in incidence trends observed in several birth cohorts among Ugandan and Zimbabwean men may be related to the introduction of ART in these populations irrespective of the age at diagnosis of HIV/AIDS (WHO, 2006). The decline in KS incidence began earlier in Uganda than in Zimbabwe, probably reflecting an earlier implementation of ART. The coverage of ART among adults increased considerably between 2006 and 2010; from 43% to 62% in Uganda and from 34% to 52% in Zimbabwe

(UNAIDS WHO, 2010). The use of ART has substantially improved the clinical outcome of patients in Western countries (Vanni et al., 2006), and in Europe, it has also been reported to reduce the risk of developing KS among patients with HIV/AIDS (Franceschi et al., 2010). Similar outcomes start to be observed in sub-Saharan Africa (Mosam et al., 2011) (Mosam et al., 2012), and further increase of ART coverage is need in this region.

Our study reported a KS incidence decrease related to HIV/AIDS prevalence decline, in Uganda and Zimbabwe, and thus suggested an important role of other factors including primary prevention. The KS decline in rates in young men (aged under 30 years) is indicative of a reduced risk in generations born after the mid-1950s in Uganda and the mid-1960s in Zimbabwe, and behavioural changes partly due to effective multiple primary prevention programmes (UNAIDS/WHO, 2011). Several reports (Stoneburner and Low-Beer, 2004), (Shelton et al., 2004), (Cohen, 2004), concluded that the primary reason for Uganda's success with regard to the control of the HIV/AIDS epidemic is the decrease in casual/multiple sexual partner behaviour. Others have suggested a prevention approach led by promotion of condom usage and HIV testing as well as the tackling of an array of broader societal factors, such as poverty, gender violence and conflict (Fenton, 2004), (Singh et al., 2003). In Zimbabwe, the success of these prevention strategies has also been reported, and has been widely associated with the HIV/AIDS decline in the country (Halperin et al., 2011).

KS incidence was 1.5 to 2.1 times higher in men, despite the lower prevalence of HIV infection among men in Uganda and Zimbabwe (International Programs Center, 2000). A sex-specific difference in risk, with incidence rates elevated among men was observed prior to the HIV/AIDS epidemic in our study. This is probably because of the higher prevalence of Kaposi sarcoma associated herpes virus (KSHV) in males (Biryahwaho et al., 2010;Dollard et al., 2010;Pfeiffer et al., 2010). In 1994, KSHV was identified in AIDS-related KS cases (Chang et al., 1994) and is now considered as the primary etiological agent for all forms of Kaposi sarcoma (International Agency for Research on Cancer (IARC), 1997). The immunosuppression caused by HIV infection increases the likelihood of other opportunistic infection including KSHV (Bouvard et al., 2009). Other factors such as a genetic predisposition of men to KS have also been postulated to explain the male predominance of this tumor. (Safai et al.,1980). In addition, the changing distribution of

KSHV infection probably also partially explained the geographical and temporal differences in KS incidence in our study. For example, we observed a higher KS incidence among women in Uganda between 2001 and 2005 compared to Zimbabwe. Concurrently, several studies have showed that KSHV infection was more frequent during this period among women in Uganda than Zimbabwe (Dollard et al., 2010), (Pfeiffer et al., 2010).

Although we used data assessed as being among the best in Africa, our study had limitations related to data quality (Curado MP et al., 2008). The percentage of morphologically verified (%MV) KS was 65% and 75% between 2002-7 in Harare and Kyadondo, respectively. The corresponding percentage of cases from death certificate only (%DCO) was 9% (between 2002 and 2007) in Harare. In Uganda, certification of death has been only carried out for legal reasons and has been known to be quite incomplete, so death certificates have not been used as a source of information by the registry. In Bulawayo, death certifications prior to burial were mandatory and the bodies of all the persons dying outside hospital in the African township of the city were brought to the mortuary for autopsy prior to certification. Between 1963 and 1967, autopsy rates were reported as 83% of all deaths in Bulawayo. In Harare (Zimbabwe) and Kyadondo County (Uganda), the low percentage of %MV (in comparison to European or American registry data quality) is a potential indicator of relative poor data validity in these registries. Some cases may be misclassified as KS. Moreover, the large %DCO observed in Harare indicated a substantial proportion of cancer cases had no information on basis of diagnosis. However, improvements in data quality were observed in both registries. In Harare, the %MV percentage increased from 60% to 65% between 1998-2002 and 2002-2007, while the %DCO decreased from 12% to 9% between the study periods.

The consistent declines in KS incidence in Zimbabwe and Uganda observed recently have been largely explained by changing patterns of HIV infection. In both countries, the combined introduction of antiretroviral therapy and effective primary prevention programmes have been the main contributing factors to the decline of HIV/AIDS prevalence, and subsequently KS incidence. General differences in KS patterns by sex, time and geographical location during the HIV/AIDS epidemic has suggested the

importance of additional risk factors, including differences in the prevalence of KSHV infection.

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Transition

Low KS and HIV/AIDS rates have been observed in Northern African populations (Section 4.1). However, UNAIDS reported an increase in HIV/AIDS prevalence in all countries of the Middle East and North Africa (UNAIDS, 2011). Furthermore, recent studies in Algeria have shown a marked increase in the prevalence of HIV/AIDS in high-risk groups, namely patients with STIs and sex workers (from 0.25% in 2000 to 2.42% in 2007 among patients with STIs and from 2.87% to 3.95% among sex workers) (Touaibia et al., 2011). Since 1998, Algeria has introduced HAART, and no studies have been published in the scientific literature on the impact of this type of therapy on the epidemiology of HIV/AIDS in the general population of Algeria.

The next article attempts to assess the impact of the introduction of HAART in 1998 on the survival of HIV-positive patients. Because time to drop-out was unknown for loss to follow-up, it was not possible to carry out a survival analysis. I have chosen to analyse the trend of standardized mortality ratios, which compare the mortality of HIV-positive patients with that of the general population, before and after the HAART era, and the trend of risk of death according to the trend of the annual proportions of HIV-positive patients receiving HAART.

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4.3 All cause mortality in HIV positive patients from six Algerian regions before and during HAART era.

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Submitted

4.3.1 Abstract

Objective: To assess mortality trends in HIV-positive patients in six regions in north-eastern Algeria before and during the highly active antiretroviral therapy (HAART) era, compared with mortality in the general population.

Methods: Standardized mortality ratios (SMRs), risk of death, and proportion of HIV-positive patients treated before and during the HAART era were calculated. The joinpoint model was used to assess the magnitude of changes in SMRs. Sensitivity analyses were performed to assess the impact on estimates of cases lost to follow-up.

Results: In 1988–2010, 156 patients were diagnosed as HIV-positive. Most patients were male (73%) and were diagnosed in 1998–2010 (74%). One third of patients were lost to follow-up. One third died, of which 83.6% died in the same year as or in the year after HIV diagnosis; median age at death (IQR) was 34.5 (11.8) years. Yearly risk of death declined from 100% in 1998 to 8% in 2010; percentage of patients treated with HAART increased from 13% in 1998 to >80% after 2002. Overall SMR decreased from 200.2 (95%CI, 123.2–325.2) before the HAART era to 91.4 (95%CI, 66.0–126.6) thereafter. From 2003, yearly SMRs decreased significantly by 66.1% ($p<0.05$) until 2006, but not thereafter.

Conclusions: Since 1998, the proportion of HIV-positive patients treated with HAART increased, reaching 84% in 2010, and mortality decreased. However, almost all patients who died during the study period seemed to be diagnosed at a late stage of the disease, emphasizing the need for earlier diagnosis of HIV in Algeria.

Key words: HIV, late presentation at diagnosis, mortality, risk of death, Algeria, North Africa

4.3.2 Introduction

The estimated HIV/AIDS prevalence in the general populations of the Middle East and North Africa (MENA) has been very low (<0.2%) (UNAIDS/WHO, 2011). In 2010, 8% of HIV-positive patients in MENA in need of antiretroviral therapy received prescribed treatment: single drug, dual-drug therapy, and/or highly active antiretroviral therapy (HAART) (UNAIDS, 2011). This proportion is higher in some countries, i.e. the percentage of adults and children living with HIV who receive prescribed treatment is estimated at 45% in Oman, 37% in Lebanon, and 30% in Morocco (UNAIDS, 2011). HAART has been available free of charge in Algeria since 1998, 14 years after the diagnosis of the first HIV-positive case (Touaibia et al., 2011). This study aimed to compare all-cause mortality of HIV-positive patients in north-eastern Algeria with that of the general population in periods before and after the introduction of HAART. To our knowledge, no previous study has assessed the evolution of all-cause mortality in HIV-positive patients over a long time period to examine the effect of the introduction of HAART into MENA. In sub-Saharan Africa, an excess mortality continues to be observed in HIV-positive patients treated with HAART; however, it might be prevented by timely initiation of HAART (Brinkhof et al., 2009).

4.3.3 Materials and Methods

4.3.3.1 Data sources

We used hospital-based data for all patients with HIV/AIDS who visited the infectious disease service in the university hospital center (CHU) of Annaba between 1 January 1988 and 31 December 2010. All such patients were included in the current study, independent of the stage of disease or the degree of immunosuppression. The CHU of Annaba is the only infectious disease service in an area covering six north-eastern wilayas (regions): Annaba, El Taref, Skikda, Tebessa, Souk Ahrass, and Guelma. It was founded in 1988, and since 1998 it has been one of the seven STI/HIV/AIDS reference centers in Algeria. Individuals with HIV/AIDS diagnosed in one of the six wilayas were almost invariably referred to the center for diagnosis, confirmation, treatment, and (active)

follow-up, and were thus captured by the registration network (Ouahdi, 2009). In 2008, the population coverage of this infectious disease service was 3,485,841 people – 10.2% of the Algerian national population (Office National des Statistiques, 2012).

From the patients' medical records, we retrieved demographic information (sex, age at diagnosis, city of origin, and date of death, where relevant), HAART use (yes or no), occurrence of cancer (site-specific), vital status in 31 December 2010 (alive, dead, or lost to follow-up), and the date of death -- date of last visit for lost to follow-up patients were not available. Data were extracted by completion of questionnaires. Patients were lost to follow-up when they missed all appointments for at least 6 months. Other variables were not considered for the analysis because of data incompleteness, e.g. information on transmission route (heterosexual mode, intravenous drug use, mother-to-child…) was not completed in all patients or viral load and CD4+ count were not tested systematically in all patients. HAART has been offered free of charge in Algeria since 1998 (Touaibia et al., 2011). HAART is defined as a combination of three antiretroviral treatments containing two nucleoside reverse transcriptase and one proteinase inhibitor or non-nucleoside reverse transcriptase inhibitor. HAART is given to the following HIV-infected patients: (a) symptomatic (e.g. weight loss >10 kg, continuous diarrhea or fever, "stage C" according to the 1993 Centers for Disease Control and Prevention (CDC) classification (CDC staff members, 1993) or oropharyngeal candidiasis); (b) asymptomatic but with CD4+ T-lymphocyte counts < 350 cells/mm3 (2006 guidelines) and then < 500 cells/mm3 (2010 guidelines) during exams performed at least 1 month apart; and (c) some specific patients, e.g. pregnant women, infected members of sero-discordant heterosexual couples, children < 2 years old, and patients with hepatitis B and/or C co-infections, with cardiovascular risks, and > 50 years old (Comité de rédaction de la Direction de la Prévention, 2010).

Because no ethical committee existed in the CHU involved in this study, the head of the infectious disease service was responsible for ethical review, and he fully approved the project. The examination of patient medical records and completion of the questionnaires were performed by those personnel who would normally have access to these records (physicians and nurses). The initials and record number of each patient were noted on the questionnaires to allow the medical professionals to find the patient's records again, if

necessary. The participants did not receive any payments, reimbursement of expenses, or any other benefits or incentives for taking part in this research..

4.3.3.2 Data analysis

Statistical analyses included descriptive statistics to compare patient demographic characteristics (sex, age at diagnosis, age at death, and city of origin), clinical characteristics (time to death, follow-up time, and proportion treated), and risk of death before (1988–1997) and after (1998–2010) the introduction of HAART. Comparisons were done using Fisher's exact test for categorical variables and Student's t test for continuous variables. Analysis comparing the characteristics of patients who were lost to follow-up with those with known status did not show significant differences in sex, age at diagnosis, city of origin, or HAART distribution (results shown in the appendix). Therefore, analyses were performed after excluding those cases lost to follow-up. Yearly of risk of death between 1988 and 2010 was calculated by dividing the number of deaths by the number of prevalent patients in a specific year. To illustrate the relationship with changes in treatment, we calculated the annual proportion of prevalent patients receiving HAART since 1998. To present annual estimates, we used three-year moving average rates to smooth out short-term fluctuations and highlight longer-term trends.

To compare mortality rates of HIV-positive patients with those of the general population, we calculated standardized mortality ratios (SMRs) between 1988 and 2010 as the ratio of the observed number of deaths in the HIV/AIDS patient cohort to the expected number obtained by applying the standard rates (all-cause mortality in the general population) to the cohort age structure. National Algerian sex- and age-specific mortality rates in 1990, 2000, and 2009 were retrieved from the Global Health Observatory and used as the reference population (WHO, 2012). For the missing annual data of 1991–1999 and 2001–2008, we performed linear interpolation of the mortality rates by sex and age. Data for 2010 were calculated from the life table produced by the Algerian National Office of Statistics (2012). Expected numbers of deaths were calculated by multiplying the number of prevalent HIV/AIDS cases by the corresponding sex-, 5-year age group-, and calendar year-specific mortality rate. 95% confidence intervals (95%CI) for SMRs were derived from the standard chi-square test (Breslow and Day, 1980).

A log-linear regression model with SMR as outcome was used to determine joinpoints in the trend. Joinpoints are breakpoints in time for which significant changes in the linear trends are detected. A maximum number of four joinpoints was specified. Standard errors of SMR (Breslow and Day, 1980) were input into the joinpoint regression program to take into account random errors in the regression model. Using joinpoints, we estimated the magnitude of the trend expressed by the annual percentage change (APC) in SMR. Because multiple tests were performed, the significance level of each test was adjusted with the Bonferroni correction by the joinpoint software to maintain the overall type I error at the specified level (0.05) (Statistical Research and Applications Branch, 2008).

To assess the validity of SMRs, we performed sensitivity analyses, mainly to evaluate the impact of patients lost to follow-up on the estimates. In the main analysis, we excluded patients lost to follow-up, and in these sensitivity analyses we performed analysis for two additional scenarios. In scenario 1, patients lost to follow-up were assumed to have died within the year of the HIV/AIDS diagnosis, and in scenario 2, patients lost to follow-up were assumed to be alive at the end of the study period. These two scenarios represent upper (scenario 1) and lower (scenario 2) bounds of possible directions of SMR trends as a consequence of including the patients lost to follow-up.

4.3.4 Results

Patient characteristics

Between 1 January 1988 and 31 December 2010, 156 patients from the six north-eastern wilayas covered by the STI/HIV/AIDS center of Annaba were diagnosed with HIV (Table 9). The center also accepted patients living outside its coverage area, i.e. 5.8% of all prevalent HIV/AIDS cases in this period came from areas outside the CHU coverage area. These cases were not excluded from the analysis. The median age at diagnosis (interquartile range; IQR) of all patients was 34.5 (11.8) years. During the study period, 55 (35%) patients died (median age at death (IQR) was 34.5 (11.8) years) and 54 (35%) were lost to follow-up. At the end of the study period, 47 (30%) of patients were alive. The majority of patients were male (73%), were diagnosed between 1998 and 2010 (74%), and were treated with HAART (89% of followed-up patients). We did not observe any significant differences between the periods before and during the HAART era in patient

Table 9 Patient characteristics for the periods before (1988–1997) and during (1998–2010) the era of highly active antiretroviral therapy.

	Period		
	1988–1997	1998–2010	
Characteristic	(*n* = 41)*	(*n* = 115)*	**p-value**
Sex			
Males, no. (%)	33 (80)	81 (70)	0.21(1)
Females, no. (%)	8 (20)	34 (30)	
Age at diagnosis* (years)			
Median (IQR)	35.0 (11.3)	34.0 (12.5)	
Min–Max	17–70	5–62	
Mean	35.8	34.8	0.63(2)
Age at death (years)			
Median (IQR)	38.0 (15.0)	37.5 (8.3)	
Min–Max	19–54	8–58	
Mean	37.6	36.9	0.79(2)
City of origin			
Annaba, no. (%)	25 (61)	52 (45)	0.30(1)
Other city in coverage area, no. (%)	14 (34)	56 (49)	
Outside coverage area, no. (%)	2 (5)	7 (6)	
Time to death (years)**			
No. of deaths (%)	17 (41)	35 (30)	
Median (IQR)	0 (1)	0 (0)	
Min–Max	0–7	0–4	
Mean	1.3	0.4	0.09(2)
Follow-up time of patients alive at the end of each period (years)**			
No. of patients (%)	4 (10)	46 (40)	
Median (IQR)	2.5 (2)	2.5 (4)	
Min–Max	1–6	0–10	
Mean	3	3.1	0.94(2)
Lost to follow-up***			
No. of patients (%)	20 (49)	34 (30)	
Risk of death, % (95%CI)**	74.0 (71.4 ; 76.3)	44.0 (42.8 ; 45.4)	0.61(1)
Proportion of patients receiving HAART, % (95%CI)**	0.0	89.0 (89.2; 89.7)	0.20(1)

* Includes all patients (alive, died, and lost to follow-up)

** Observed rate excluding patients lost to follow-up

*** Lost to follow-up: missed all appointments for at least 6 months

(1) Fisher's exact test

(2) Student's t test

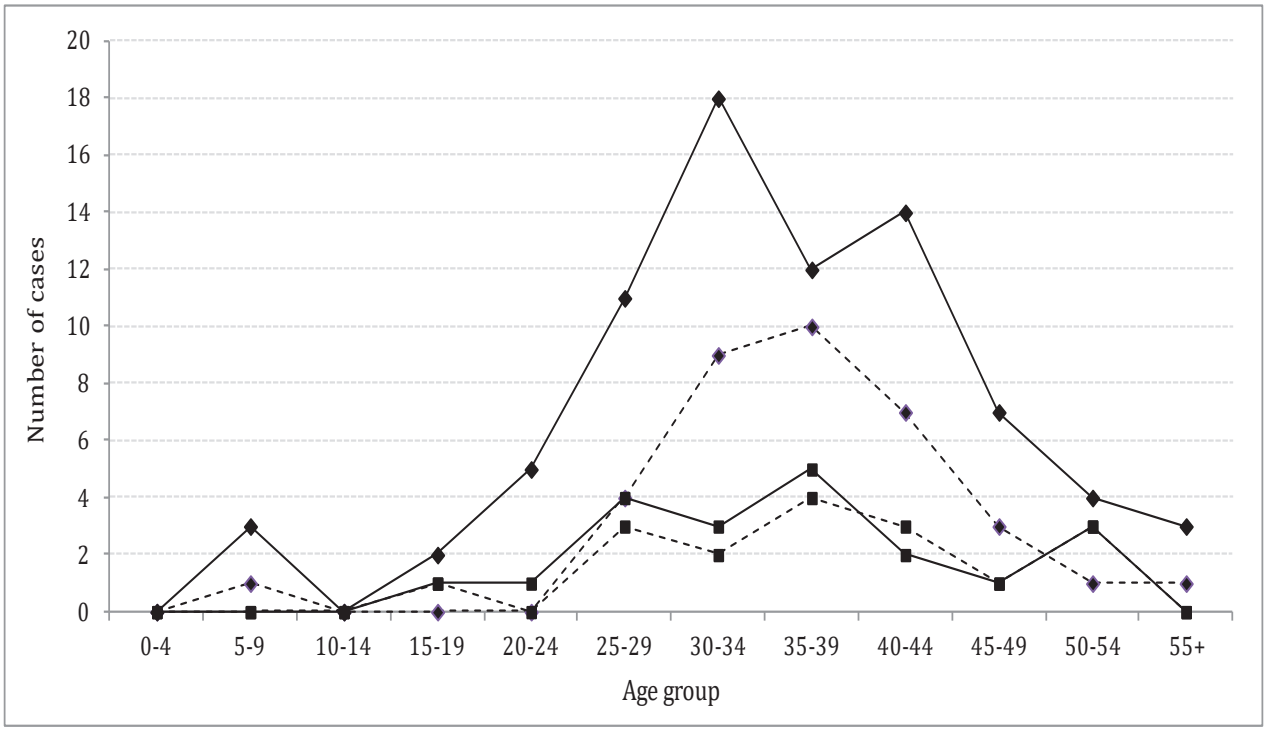
95%CI, 95% binomial confidence interval relying on approximating the binomial distribution with a normal distribution; HAART, highly active antiretroviral therapy; IQR, interquartile range.

age at diagnosis, age at death, sex distribution, city of origin, time to death, or follow-up time of patients alive at the end of the study period.

During the pre-HAART era, 2 cases of Kaposi sarcoma (KS) were diagnosed among the 41 HIV-positive patients (5%). After the introduction of HAART, 2 cases of KS and 1 case of female breast cancer were diagnosed among the HIV-positive patients (2% and 1% of HIV-positive patients, respectively). For the KS cases, the skin lesions were localized to the extremities and the face and were responsible for the diagnosis of both cancer and HIV. The breast cancer was diagnosed 1 year after HIV diagnosis.

During the HAART era, the majority of patients who died did so in the same year as or in the year after their HIV diagnosis (84%). Their demographic characteristics were similar to those of the overall population studied: 79% were male, median age at diagnosis (IQR) was 36 (10.3) years, and 46% were from the city of Annaba. However, the only difference observed between these patients and the rest of the study population is the lower proportion of patients receiving HAART (63% vs 94%). Figure 18 shows the number of diagnosed cases and the number of deaths, by 5-year age group, for the periods before and during the HAART era. The curves showing the number of diagnosed cases and deaths were similar in shape, with a peak in the 35–39 year age group during the pre-HAART period; thereafter, for the number of diagnosed cases only, the peak was in the 30–34 year age group.

Figure 18: Newly diagnosed HIV/AIDS cases and number of deaths by age group before (1988–1997) and during the HAART era (1998–2010) in north-eastern Algeria.

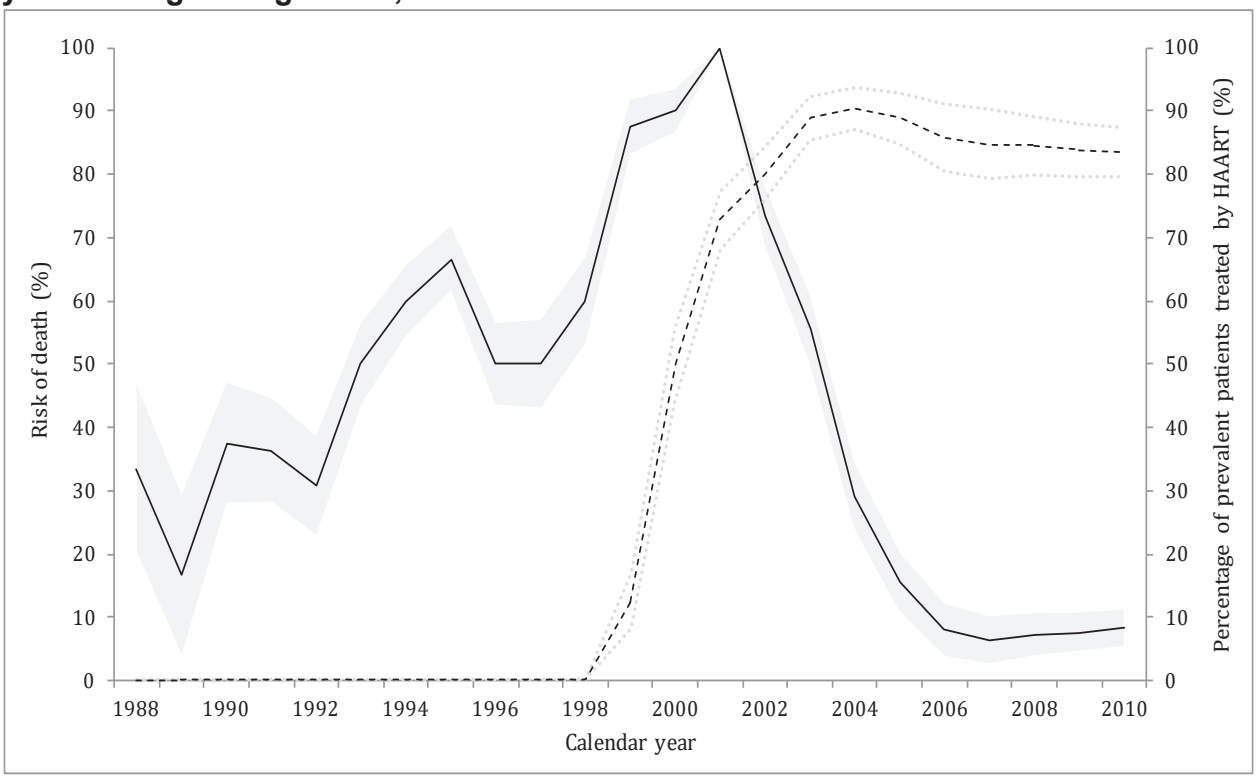


Solid lines, number of HIV-diagnosed patients in 1988–1998 (squares) and 1999–2010 (diamonds); **dashed lines**, number of deaths in 1988–1998 (squares) and 1999–2010 (diamonds). Patients lost to follow-up were excluded.

Overall risk-of-death and standardized mortality ratios

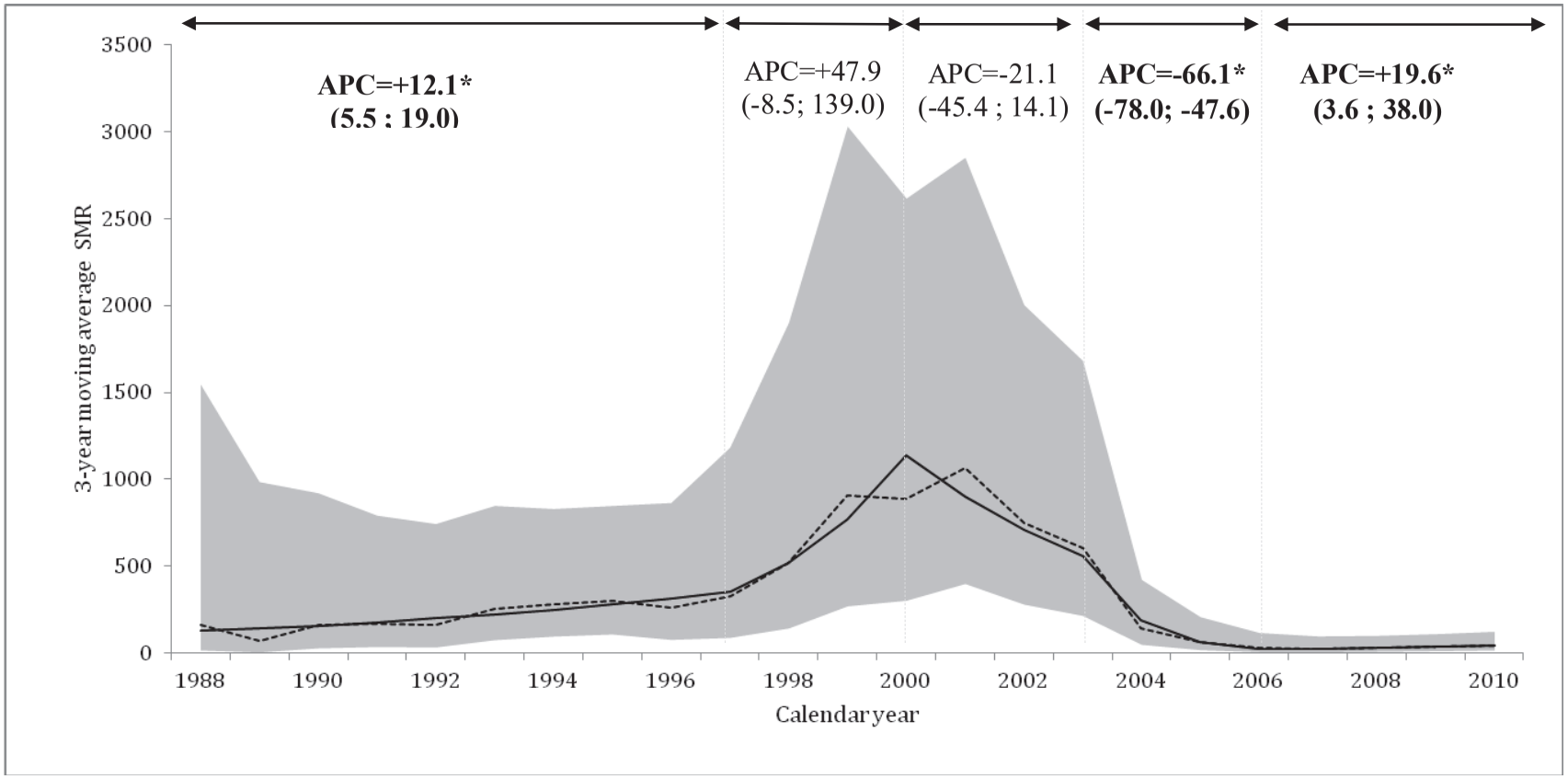
Figure 2 shows the yearly risk of death over time, together with the proportion of patients receiving HAART. The risk of death increased from 33% in 1988 to 100% in 2001 and then decreased to 8% in 2010; this marked decline coincided with an increase in the proportion of patients receiving HAART, which increased from 13% in 1998 to 84% in 2010 (Fig. 19). The overall SMR declined from 200.2 (95%CI: 123.2–325.2) during the pre-HAART era to 91.4 (95%CI: 66.0–126.6) during the HAART era. The annual SMR trend derived from the joinpoint model is shown in Figure 20; it consists of five line segments joined at the joinpoints of 1997, 2000, 2003, and 2006. SMRs increased significantly until 1997 (APC = +12.1; 95%CI = 5.5 to 19.0), remained steady until 2003, and then decreased significantly (APC = –66.1 ; 95%CI = –78.0 to –47.6) until 2006, with only a modest increase thereafter.

Figure 19: Trends of the risk of death and use of highly active antiretroviral therapy (HAART) among HIV/AIDS patients in the university hospital center of Annaba, 3-year moving average rates, 1988–2010.



Solid line, risk of death; ***dashed line***, percentage of prevalent patients treated by HAART; ***gray area and gray dashed line around line***, 95% confidence interval.

Figure 20: Standardized mortality ratios (SMRs) and annual percentage change (APC) in SMR between 1988 and 2010.



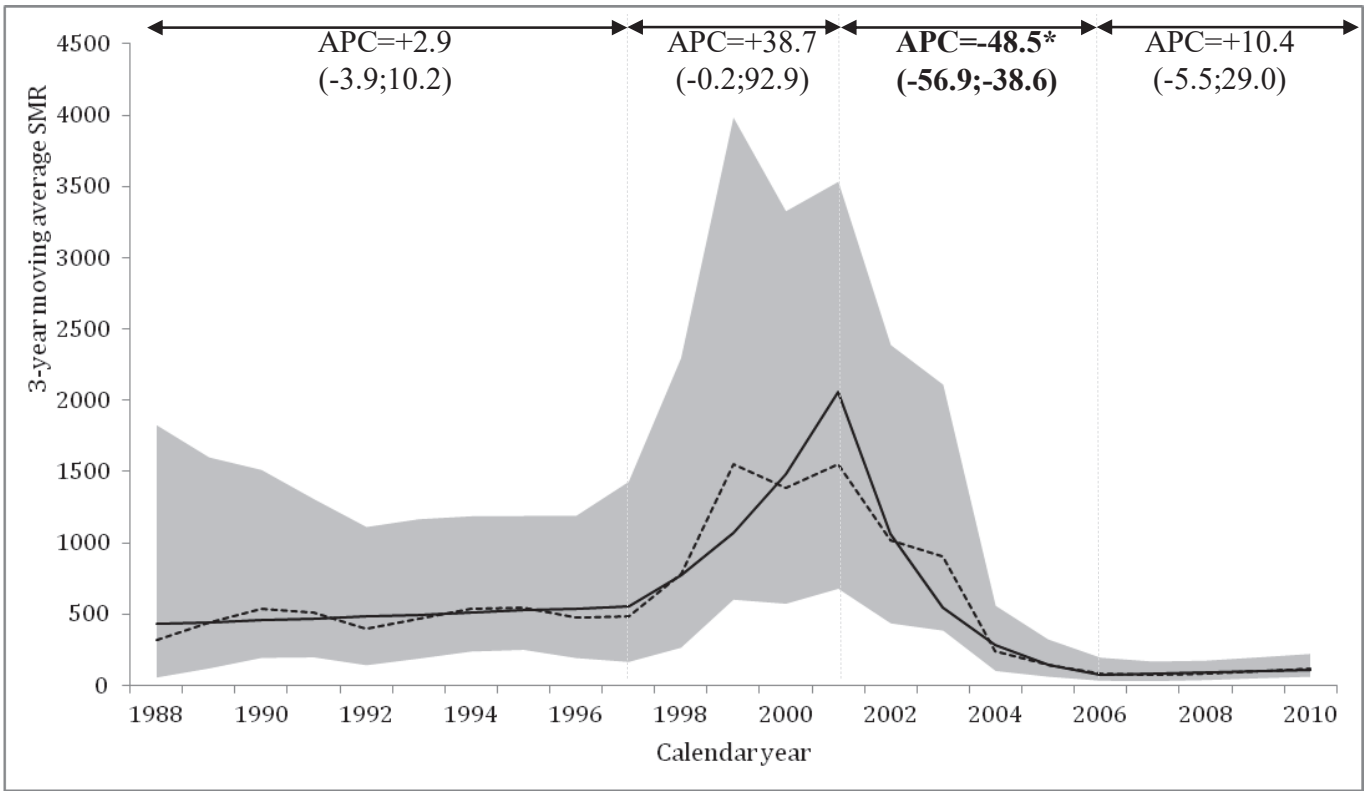
Dashed line, 3-year moving average SMR; ***solid line***, modeled curve; ***gray area around line***, 95% confidence interval of SMR. *Annual percentage change (APC) was significant with p-value<0.05.

Sensitivity analysis

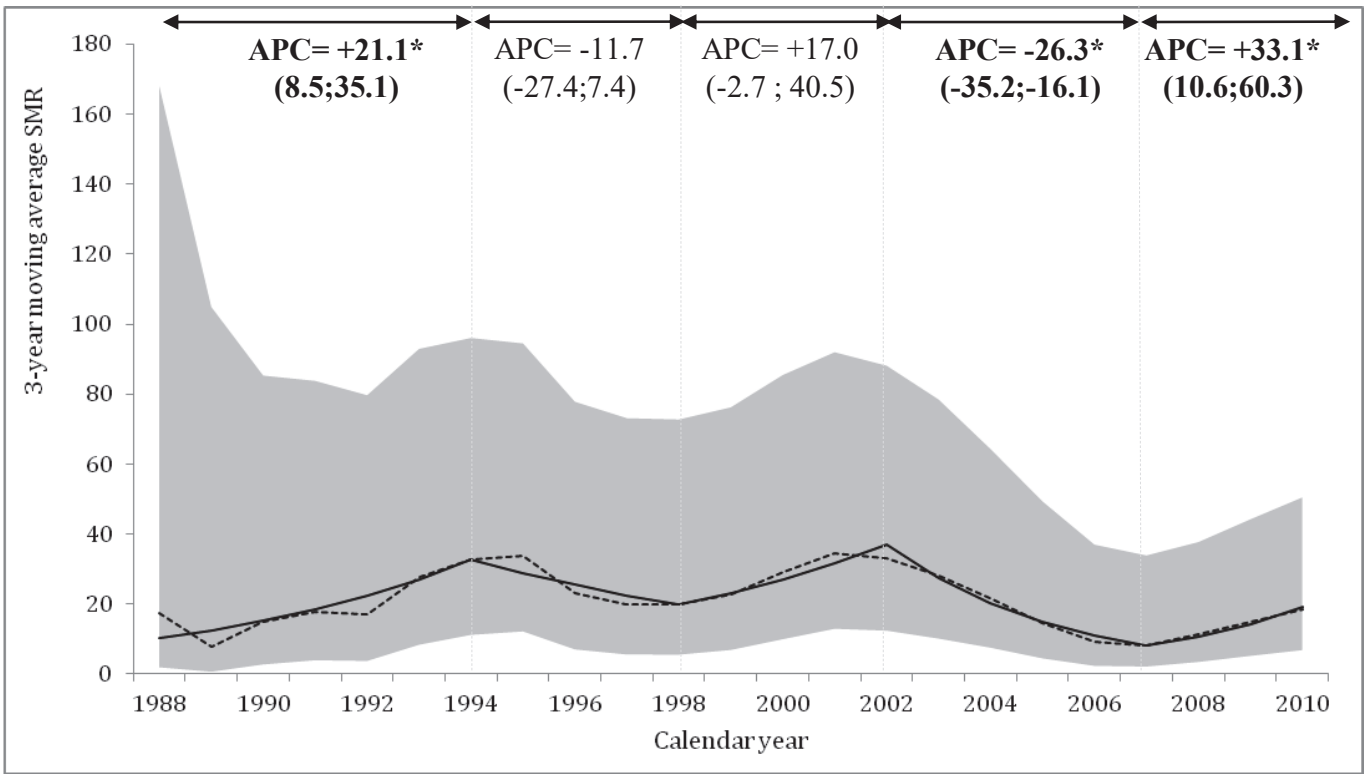
The sensitivity analysis shows that the SMRs of the upper-bound scenario (Fig. 21a), in which patients lost to follow-up were assumed to have died within a year of the HIV diagnosis, were considerably higher than the estimates in the main approach, whereas the SMRs of the lower-bound scenario (Fig. 21.b), in which patients lost to follow-up were assumed to be alive at the end of the study period, were considerably lower than the estimates in the main approach. The estimated APC before the HAART era also shows contradictory results, with a significant increase in SMRs before the HAART era in the lower-bound scenario and stable SMRs in that period in the upper-bound scenario. However, in spite of this, these two extreme assumptions both demonstrate a significant decrease in SMRs starting in the early 2000s.

Figure 21: Sensitivity analysis for standardized mortality ratios (SMRs) between 1988 and 2010. (a) Scenario 1: patients lost to follow-up were assumed to have died within the year of HIV/AIDS diagnosis. (b) Scenario 2: patients lost to follow-up were assumed to be alive at the end of the study period.

a- Scenario 1



b- Scenario 2



* Annual percentage change (APC) was significant with p-value<0.05. ***Dashed line***, 3-year moving average SMR; ***solid line***, modeled curve; ***gray area around line***, 95% confidence interval of SMR

4.3.5 Discussion

This study reports changes in HIV/AIDS mortality rates in six north-eastern Algerian wilayas over a 23-year period. The risk of death among HIV-positive patients decreased from 100% to 8%, while the proportion of patients treated with HAART increased from 13% to 84%. Decreasing mortality was also observed when HIV/AIDS patients were compared with the general population, in which relative mortality rates have decreased significantly since 2000. However, mortality rates among HIV/AIDS patients continued to be higher than that of general population in north-eastern Algerian (SMR = 91.4) after the introduction of HAART.

During the HAART era, one third of HIV-diagnosed patients died, most of them within 2 years after diagnosis. The only difference observed between these patients and the rest of the study population is the lower proportion of patients receiving HAART (63% vs 94%). During the HAART era, median time to death and median follow-up time of patients alive

at the end of the study period who were diagnosed during the HAART era were less than the median survival time from enrolment to death for prevalent cases (4.5 years) in the HIV-1 natural history cohort 5-year prospective study in the rural Masaka district of Uganda which ended in 1995 (Morgan et al., 1997), where HIV prevalence in adults was 8% and no antiretroviral therapy was available (WHO, 1995). Late stage of disease at diagnosis could explain the relatively short time to death in the patients of the current study and lower HAART prevalence. Furthermore, lack of adequate therapy might be an additional explanation for the failure to limit disease progression for some of the patients. Triple therapy (HAART) has been used in Algeria as first- and second-line treatment, yet there is currently no validated therapeutic approach for third-line treatment (Comité de rédaction de la Direction de la Prévention, 2010). Unlike in Europe, fusion inhibitors, CCR5 inhibitors, and integrase inhibitors are not currently in use in Algeria (Yeni, 2010).

Despite the reported low prevalence of HIV/AIDS in Algeria, the number of diagnosed patients has tripled during the HAART era compared with the pre-HAART era. In 2000, the first national HIV sero-surveys were conducted among pregnant women, sex workers, and drug users, followed by surveys in 2004 and 2007 (Fares and Mokhtari, 2001;Fares and Mokhtari, 2005;Fares and Mokhtari, 2008). Across the country, 54 testing centers were opened in 2006, which referred patients identified as HIV-positive to the STI/HIV/AIDS centers (Ouahdi, 2009). Part of the increase in diagnosed cases in our study was probably an artifact of increasing awareness among medical professionals, but this result likely also reflects a genuine increase in HIV/AIDS cases. Among the general population, knowledge of HIV/AIDS is very poor, as shown in two surveys conducted among students in Algeria (Abdennour, 2012b), (Abdennour, 2012a), so this is unlikely to motivate a reduction in high-risk behaviors that lead to increased risk of HIV transmission. Furthermore, a recent study in two hospitals in north-eastern Algeria reported an HIV prevalence of 5.3/1000 among pregnant women (Aidaoui et al., 2008).

In other countries such as Zimbabwe and Uganda, the decline of the HIV/AIDS epidemic has been attributed to increased access to antiretroviral treatment coupled with active prevention campaigns to increase population awareness and change risk behaviors (UNAIDS/WHO, 2011), (UNAIDS WHO, 2010), (Halperin et al., 2011). In sub-Saharan African countries, the mortality of HIV-infected patients treated with HAART continues to

be higher than that in the general population, but for patients with CD4 count ≥200 cells/ml and starting HAART with the best prognosis excess mortality was moderate and mortality reached that of the general population in the second year of receiving HAART. Much of the excess mortality might be prevented by timely initiation of HAART (Brinkhof et al., 2009). Algerian public health policy should continue to encourage early detection programs, especially among young males, who were the most affected group because of use of sex-worker services. Furthermore, because heterosexual intercourse is the primary mode of HIV transmission in Algeria (98%) (Touaibia et al., 2011), the spread of HIV in families is of great concern. Therefore, pregnant women might be another potential target group for early prevention, to avoid mother-to-child transmission (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1996) and improve the prognosis of the unborn children (Siegfried et al., 2011).

One of the limitations of our study is the large number of patients lost to follow-up. It is very probable that some of these patients had died, and thus the number of deaths may be underestimated in the main analysis. However, the sensitivity analysis, including extreme scenarios, confirmed the decrease in mortality among HIV-diagnosed patients after the introduction of HAART. Furthermore, the small number of cases in the current study means that we have limited power to examine some associations. In addition, for some patients the long distance from their residence to the STI/HIV/AIDS reference center may cause these patients to go to closer reference centers. However, based on a report of a neighbouring center (Setif), no cases from the Annaba center were followed up there (Lacheheb, 2007). Social stigma and physician reputation may also influence patient preferences in selecting a care provider. Of the study patients, 5% came from outside the center's coverage area, and we expect that a similar proportion of patients went outside the Annaba coverage area for care. Finally, because we observed a noticeable proportion of patients diagnosed in the late stage of the disease, a number of patients who died of HIV without being diagnosed and referred to the STI/HIV/AIDS reference center were probably missed in the current study.

This study showed a decrease in the all-cause mortality rate after the introduction of HAART in 1998 for HIV-diagnosed patients, for which the proportion of patients receiving

HAART reached 84% in 2010. However, the mortality rate remained higher than that of the general population. Almost all patients who died during the study period seemed to be diagnosed in the late stage of the disease. Public health programs encouraging early detection of HIV in Algeria should be coupled with the increasing proportion of patients treated with HAART to reduce risk of death among patients with late-stage disease.

4.3.6 Reference

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4.3.7 Appendix

The following results (Table 9 and 10) present the comparison between on the one hand lost to follow up and living patients and on the other hand lost to follow up and died patients.

During the data management of the current study, 7 patients (4.5% of all patients; one diagnosed in 1988-1997 and 6 diagnosed in 1998-2010) where classified in the loss to follow up subgroup even if I know they died, because the date of death was unknown. It was impossible to calculate their times to death..

Because I wanted to know whether lost to follow up patients were different from living and dead patients, these 7 dead patients with missing data on the date of their death, were included in the dead patient subgroup in the following tables.

No significant differences in demographic characteristics (sex, age at diagnosis and location) and in the proportion of patients receiving HAART were observed between loss to follow up subgroup and the two other subgroups (Table 9 and 10).

Tableau 10: Demographic characteristic of HIV/AIDS patients who were alive, dead and lost to follow-up during the whole period study (1988-2010) in both sexes, in North-eastern Algeria

	Lost to follow-up*		Alive		p-value	Died		p-value
	Total	(%)	Total	(%)		Total	(%)	
Age at diagnosis								
Min-Max	8-70		5-59			7-58		
Mean	33.9		34.87			36.03		
Median	33.5		34			37		
No	46		47			63		
5-30	15	(33)	16	(34)		13	(21)	
30-40	20	(43)	14	(30)	0.178	30	(48)	0.219
40-70	9	(20)	17	(36)		20	(32)	
Unkown	2	(04)	0	(00)		0	(00)	
Sex								
Males	34	(74)	26	(55)	0.052	54	(86)	0.123
Females	12	(26)	21	(45)		9	(14)	
Location								
Annaba	22	(47)	21	(45)		33	(53)	
ElTaref	8	(17)	3	(06)		7	(11)	
Guelma	5	(11)	1	(02)		3	(05)	
Skikda	1	(02)	5	(11)	0.745	6	(10)	0.419
Soukahras	2	(04)	9	(19)		3	(05)	
Tebessa	2	(04)	4	(09)		8	(13)	
Outside coverage area	3	(10)	4	(10)		2	(03)	
Unknown	3	(07)	0	(00)		1	(02)	

No=Number of patients; Unknown: Missing data (if <5%. missing data was dropped); time periods = years of HIV diagnosis; Lost to follow-up: missing all appointments for at least 6 months; *date of lost to follow-up is unknown

Tableau 11: Highly active antiretroviral (HAART) use in HIV/AIDS patients who were alive, dead and lost to follow-up during the whole period study (1988-2010) in both sexes, in North-eastern Algeria

	Lost to follow-up*		Alive		p-value	Died		p-value
	Total	(%)	Total	%		Total	%	
HAART								
No	30	(65)	8	(17)		36	(57)	
Yes	13	(28)	38	(81)	0.651	26	(41)	0.723
Unknown	3	(07)	1	(02)		1	(02)	

HAART: Highly active antiretroviral therapy; No=Number of patients; Unknown: Missing data (if <5%. missing data was dropped); time periods = years of HIV diagnosis; Lost to follow-up: missing all appointments for at least 6 months; *date of lost to follow-up is unknown

Transition

The previous article (Section 4.3) showed 33% of patients died during the study period; among them, 83.6% died in the same year as, or in the year after, their HIV diagnosis.

Late presentation of HIV/AIDS at diagnosis was suggested to explain this high percentage of patients presenting with a short time to death after their HIV diagnosis. To confirm that these patients were really at the late stage of the disease, data on CD4+ count were needed. Unfortunately this variable was not available in all medical records. The following case report illustrates the very late stage of the disease that could be observed at diagnosis in north-eastern Algeria. This case report provides further insight into the identification of the HIV/AIDS profile of patients in north-eastern Algeria.

4.4 A case of very late stage of HIV/AIDS at the diagnosis in North-eastern Algeria: a need of increase awareness and early detection.

Chaabna K; Laouar M; Boudiaf Z; Vanehms P; Roubhia S; Soerjomataram I.

Submitted

4.4.1 Abstract

This case report describes a case of an HIV-positive adult man diagnosed at a very late stage of AIDS in Annaba, Algeria. He died one week after his HIV/AIDS diagnosis, in 2004. This patient was an intravenous drug user diagnosed as hepatitis C virus (HCV)-positive since 1983. Epidural abscess and thoracic zoster were observed one decade before his HIV/AIDS diagnosis. He was directed to a specialized medical service after continuous fever and after four months of chronic diarrhoea, unresponsive to treatment. He presented with Kaposi sarcoma skin lesions and HIV-associated myelopathy. This case reveals the real difficulties that some medical professionals have in making a diagnosis of HIV infection at an early stage of the disease. Highly active antiretroviral therapy has been available free in Algeria since 1998. Treatment access should be coupled with more active prevention campaigns to increase physician and population awareness and change HIV risk behaviours..

Key words: HIV, late stage of AIDS, Kaposi sarcoma, HCV, Algeria, MENA, Africa

4.4.2 Introduction

The estimated HIV/AIDS prevalence in the general population in the Middle East and North Africa (MENA) is low (<0.2%) (UNAIDS/WHO, 2011). However, since 2001 the number of people newly infected with HIV in MENA has increased by >35% (UNAIDS, 2011). This case illustrates the very late presentation of HIV/AIDS patients observed in north-eastern Algeria.

4.4.3 Clinical presentation

The patient was a 47-year-old man from Annaba (Algeria). He was an intravenous drug user with chronic hepatitis C (HCV) infection that was first diagnosed in 1983. He had surgeries in France for haemorrhoids in 1979 and 1984 and for epidural abscess in 1983, and he had thoracic zoster in 1991. In addition to drug use, these surgeries performed before 1990 in France, where HCV nosocomial transmission existed, could be potential HCV and HIV transmission risk factors.

He presented with continuous fever (38.5 °C) and a four-month history of chronic diarrhoea, unresponsive to treatment, causing asthenia, mucocutaneous pallor, and 18kg weight loss. He was diagnosed as HIV-positive one week before his death, in 2004. A test for Koch bacillus was negative, excluding pulmonary tuberculosis.

Clinically, the patient had skin lesions localized to extremities, legs, and external genital organs, with a swollen, painful, hyper-pigmented, and oedematous scrotum. These skin lesions were angiomatous and erythromatous, mostly purple, sometimes nodular and sometimes confluent. Kaposi sarcoma was confirmed by lymph node biopsy.

Neurological examination revealed pyramidal syndrome with a positive Babinski reflex, deep tendon hyper-reflexia, claudication, paresthesia of the left lower limb with pain, and disorder of the surface sensitivity of the upper extremities with numbness and functional impairment (due to narrow spinal canal), suggesting HIV-associated myelopathy.

Rheumatological examination revealed limited bending and movement of fingers, myalgia and arthralgia in the left leg, and painful pressure in the first cervical vertebrae.

Gastrointestinal examination revealed diarrhoea with fresh blood and mucus, melena, upper abdominal pain and colic, and ascites. Digital rectal examination showed external haemorrhoids, tonic activity of the anal sphincter, and two polyps of 1 cm diameter

localized at the anterior surface of the rectum. Esophagogastroduodenoscopy, colonoscopy, and proctoscopy revealed intestinal and rectal polyposis. Biopsy characterized the rectal polyps as adenomatous, well differentiated. Abdominal ultrasonography showed discrete splenomegaly.

Gastroduodenal biopsy revealed partial villous atrophy associated with signs of duodenitis; ileal and colonic mucosa showed inflammation and were richly vascularized, suggesting Helicobacter pylori infection, but serological testing to confirm this was not performed.

Ascites are one symptom of cirrhosis in chronic HCV infection. A positive Rivalta test of ascetic fluid removed after puncture suggested high concentrations of protein and inflammatory mediators; however, fibrinogen concentration was not significantly high (4.2 g/L). The volume of removed fluid was not specified. The fluid was clear during the first puncture, and turbidity was observed on subsequent examinations. Albumin concentration was 6g/L; amylase concentration was 4U/L. Serum hypoalbuminemia (12.7 g/L) could suggest poor liver function; however, it could be related to malabsorption due to the patient's chronic diarrhoea. Aspartate aminotransferase was high (54 U/L); alanine aminotransferase (20 U/L) was normal.

White blood cell count (4260/mm3) was within normal limits but with a high polymorphonuclear neutrophil count (2810/mm3), normal monocyte count (220/mm3), and low lymphocyte count (120/mm3). C-reactive protein level was 24mg/L, suggesting mild inflammation and viral infection (Clyne and Olshaker, 1999). Fibrinogen (4.2g/L) was slightly higher than the upper limit of the normal range (2–4 g/L).

Complete blood count revealed a high red blood cell count (9 million/mm3), normal platelets (193/mm3), and low haemoglobin (8.9 g/dL) and haematocrit (29.8%); mean corpuscular volume (97.4 fL) was at the upper bound of the normal range, and mean corpuscular haemoglobin concentration was normal (30 g/dL), suggesting a diagnosis of anaemia. No further test was done to differentiate macrocytic and microcytic classes of anaemia. In addition, a myelogram showed vitamin B12 and folic acid deficiencies, possibly suggesting the megaloblastic subtype of macrocytic anaemia. Macrocytes could be the product of marrow megaloblastic precursors (vitamin B12 or folic acid deficiencies) or of normoblast precursors (alcoholism, liver disease) (Davenport, 1996) Observed

neurological abnormalities and central nervous system impairment suggested vitamin B12 deficiency as the main causal factor for the anaemia. The vitamin B12 deficiency could be explained by HIV or Helicobacter pylori infection (Kaptan et al., 2000).

The patient received co-trimoxazole as prophylaxis against opportunistic infections, human albumin for hypoalbuminemia, loperamide for diarrhoea, and vitamin B12 to treat anaemia. The patient died one week after his HIV/AIDS diagnosis, and he received neither antiretroviral therapy for HIV infection nor HCV treatment.

4.4.4 Discussion

The patient had HIV/AIDS with late-stage symptoms, including HIV-associated myelopathy and Kaposi sarcoma. He was also diagnosed with chronic HCV infection, with hepatic cirrhosis, rectal adenoma, anaemia, and vitamin B12 deficiency.

This case report illustrated a HIV-positive patient diagnosed at a very late stage of AIDS, probably with long-term HIV seropositivity. Identified as a intravenous drug user with chronic HCV infection, this patient belongs to a high-risk group for HIV transmission, but he was only diagnosed as HIV-positive after four months of chronic diarrhoea, unresponsive to treatment, and one week before his death. Epidural abscess and thoracic zoster, which were observed in this patient one decade before his HIV/AIDS diagnosis, and HIV-associated myelopathy are usually noted in patients with long-term HIV infection (at least ten years) (Moulignier, 2006), suggesting that the patient may have been HIV-positive for many years. This may reveal the difficulty of making the correct diagnosis of HIV infection at an early stage of the disease Algeria because the infection is rare and because medical professionals have a poor awareness of HIV/AIDS infection. The patient was married and had one child. Because condoms are rarely used as contraception among married couples in Algeria (Aidaoui et al., 2008), there was a high risk of intra-family transmission (both intracouple and mother-to-child). Therefore, public health authorities should consider how to improve early detection of HIV/AIDS. Highly active antiretroviral therapy has been available free in Algeria since 1998 (Comité de rédaction de la Direction de la Prévention, 2010); early detection of HIV-positive patients should contribute to increasing their life expectancy and preventing HIV transmission. The increasing trend of HIV infection in MENA countries such as Algeria highlights the growing

need for increased awareness of the risk of the spread of HIV/AIDS in the general population.

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Transition

One of the main results in the article on the geographical patterns of KS, NHL, and cervical cancer in five African populations (Section 4.1) was the markedly high NHL incidence in Egypt relative to the other northern African and sub-Saharan African populations. We observed that despite the fact that HIV infected about one third of the Zimbabwean population, NHL incidence was lower than in Egypt, where the prevalence of HIV/AIDS was less than 2% during the time period studied. In the discussion, I have suggested that the high NHL incidence in Egypt was related to the high HCV prevalence.

I wanted to assess the situation in another northern African population. Nothing has been published in the scientific literature about NHL and HCV in Algeria. Therefore, I chose the eastern Algerian population. Contact was made with the regional haematological service of the CHUs of Annaba and Batna, and I went there to perform a retrospective study.

Between January 2009 and December 2010, 98 NHL cases were diagnosed in the Annaba region (40 in 2009 and 58 in 2010) and NHL was more frequent among men (63.3%). Serological tests among these NHL patients diagnosed two cases of HCV infection and two cases of HBV infection (no co-infection or HIV infection). Unfortunately, 31.6% (31/98) of NHL patients were not tested for HCV, HBV, or HIV infection. Thus, because of the high percentage of unknown serology it would be difficult to conclude anything from these observations about the prevalence of HCV among NHL patients living in the Annaba region.

In Batna, during the same period, 36 NHL cases (28 B-cell subtype and 8 T-cell subtype) were diagnosed, and all of these patients were tested for HCV, HBV, and HIV. NHL was more frequent in women (77.8%, 28/36). HCV infection was diagnosed in 2 patients with B-cell NHL (5.6% of NHL cases and 7.1% of B-cell NHL cases). No HBV or HIV infections were found among these NHL patients.

Although it is difficult to disentangle causality using case reports and case series, they may lead to the formulation of new hypothesis. As such, case reports and case series represent an important interface between clinical medicine and epidemiology. Hennekens also added that “this design has historical importance in epidemiology, as it was often

used as an early means to identify the beginning or presence of epidemic" (Hennekens and Buring, 1987).

The following accepted case report is the first paper about NHL and HCV in Algeria, and I hope it will increase awareness in Algerian public health professionals of this public health problem. Systematic serological tests in all the Algerian haematological services should be introduced in the protocol of NHL patient management before the implementation of chemotherapy. This retrospective study showed that infection of NHL patients with hepatitis viruses is a reality, and that HCV may be an etiological agent for this lymphoma in Algeria.

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4.5 Co-occurrence of diffuse large B cell non-Hodgkin lymphoma and chronic hepatitis C in Algerian patients: two case reports

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4.5.1 Abstract

For the first time in Algeria, we report on the presentation, diagnosis and management of two cases of diffuse large B cell NHL with chronic HCV infection. Both Algerian patients came for medical consult without HCV-related symptoms. Systematic serological tests to identify HIV and hepatitis B and C infections which performed on all patients led to HCV diagnosis. Chemotherapy was given to both patients without exacerbation of the HCV infection. These observed cases shed new light on the possible pathogenesis of NHL in Algerian population. Indeed, in Algeria, HCV may partly been responsible of the unexplained increase of NHL incidence in Eastern region of Algeria especially among those who are frequently exposed to HCV risk factors (haemodialysis and dental care). Furthermore, our observations underscore the importance of prevention programmes including screening to control HCV in Algeria.

Key words: Algeria, cancer, hepatitis C, infection, non-Hodgkin lymphoma

4.5.2 Introduction

In Batna, Algeria Non-Hodgkin lymphoma (NHL, C82-C85;C96) incidence has increased between 1995 and 2008 (Bouhidel, 2011). The causes of this increase remain unknown. Extra-hepatic cancers, related to hepatitis C Virus (HCV), have only recently been identified (Bouvard et al., 2009). Here for the first time in Algeria, we report on two HCV cases in B-cell NHL patients identified in the hematological service of Batna Regional University Teaching Hospital. This report aims to suggest hypothesis on the increasing incidence of NHL in Eastern region of Algeria.

4.5.3 Clinical presentation and intervention

Patient 1: The patient was a 66-year-old woman admitted to the hematological service for treatment of diffuse large-cell lymphoma in 2010. A fever accompanied by intense fatigue and profuse night sweats led her to consult. During physical examination, lower left cervical lymphadenopathy was detected. Lymph node biopsy followed by histological study and completed by immunohistochemistry led to the diagnosis of large B-cell non-Hodgkin lymphoma (CD45 and CD20 positive).

Blood viral test were negative for human immunodeficiency virus (HIV) and hepatitis B (HBV), but positive for HCV (subsequently confirmed by polymerase chain reaction). The virus was genotyped as 1b using the Versant Lipa genotype assay (Siemens, 2011). Several potential HCV transmission factors were identified in this patient. She has had seven births, one induced abortion and several dentist visits. The presence of traditional piercings and tattoos was also noted. However, there was no history of dialysis, intravenous drug use, blood transfusion, hospitalization, surgery, endoscopy or occupational exposure.

Clinically, the patient had a lower left cervical lymphadenopathy and a left axillary lymphadenopathy 4cmx4cm and splenomegaly with a 16cm overhang. A computed tomography - scan (CT-scan) showed heteronodular splenomegaly, hepatomegaly and hilar lymphadenopathy of the liver and the spleen. The chest radiology was normal. The blood count showed leukocytosis (13,500/mm3) predominantly granulocytic (10,400/mm3), moderate anemia (haemoglobin Hb: 9.4g/dl), normochromic, normocytic

and normal platelet count. Furthermore, the presence of inflammation was observed with erythrocyte sedimentation 117mm/min; high fibrinogen 5.33g/l. Lactate dehydrogenase (LDH) level was elevated (1125 UI/l) and aminotransferase were normal. Gamma GT and alkaline phosphatase were not quantified. Moreover, blood analyses showed hypoalbuminemia (31g/l) but normal glucose, urea and creatinine level.

The patient received 8 cycles of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) which achieved a complete remission of NHL. Maintenance treatment with quarterly monoclonal anti-CD20 antibody Rituximab is underway. No clinical sign of progression of hepatitis C was observed during treatment of the NHL i.e. no jaundice nor liver tenderness on palpation and normal level of aminotransferases. For economic reason patient received no treatment for the HCV infection.

Patient 2: The patient was a 63-year-old woman who has had type II diabetes since the age 59 years and hypertension for 23 years. The first symptoms began in 2009, including sore throat with tonsillar hypertrophy, fever, dysphagia, dysphonia and snoring, and finally the patient came for medical consult in 2010.

Upper jugulo-carotidid lymphadenopathy and a significant increase in the volume of the right amygdala (tumour-like) were found during Ear, Nose and Throat (ENT) consultation. Biopsy and histological study of the amygdala led to a diagnosis of diffuse large B cell non-Hodgkin lymphoma, with intense and diffuse expression of CD20 and CD45.

Viral serologies showed that the patient was HIV- and HBV-negative but HCV-positive (subsequently confirmed by PCR). Identified HCV transmission factors included nine deliveries, one induced abortion, dental care, and piercings and traditional tattoos. No history of dialysis, intravenous drug use, blood transfusion, hospitalization, surgery, endoscopy or occupational exposure was noted.

The patient's hemogram was within normal limits with no signs of inflammation. Furthermore, renal function and level of protein and albumin were normal. CT-scan of the oropharynx showed a right tonsillar tumour tissue thickening with large compressive carotid-jugular lymphadenopathy and a heterogeneous densification of the thymic lodge. The thoracic and abdominal scans were normal, as was the bone marrow biopsy.

After six cycles of R-CHOP, patient had a complete remission of lymphoma. Maintenance treatment has been scheduled but not performed because of patient refusal. During the

induction treatment, no progression of hepatitis C was observed i.e. no clinical sign of hepatitis activity (jaundice or liver tenderness on palpation). No treatment against HCV infection was planned due to patient' psychiatric problem.

4.5.4 Discussion

We report two cases of large B cell NHL with complete remission after R-CHOP treatment, who concurrently had a chronic hepatitis C. Chemotherapy did not increase HCV ribonucleic acid (RNA) levels nor aggravate hepatic lesions in these patients. Unfortunately, due to co-existing disease and economic reason, patients did not receive treatment for the HCV infection i.e. pegylated interferon alpha and Ribavirin.

In Algeria, the prevalence of HCV in the general population was low(Ayed et al., 1995;Berkane, 2003); although much higher prevalence in haemodialysis patients has been described (40.7%) (Bensalem et al., 2011). In this report both patients have very similar risk factors for HCV transmission; exposure to blood products, supporting previous studies which have highlighted the importance of nosocomial transmission in Algeria(Berkane, 2003);(Zemouli et al., 2011). Our observations emphasize the importance of preventive programmes including screening to control HCV spread in this country.

The aetiology of NHL is complex and has been associated with different viruses including EBV, HHV-8, HIV, HTLV-1 as well as HCV (Bouvard et al., 2009);(Dal and Franceschi, 2006). These observed cases shed new light on the possible pathogenesis of NHL and they may partly explain the emergence of NHL especially among those who are frequently exposed to medical procedures in Algerian population.

HCV is an established cause of NHL; however our case study raises the concern whether it is the major factor behind the recent increase of haematological malignancy in Algeria.

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5 General discussion

5.1 Main results and Hypothesis

The African continent can be divided into two geographical areas based on the HIV/AIDS prevalence relative to worldwide prevalence rates: northern Africa, which has a lower HIV/AIDS prevalence, and sub-Saharan Africa, which has a higher prevalence. Furthermore, among sub-Saharan African populations HIV/AIDS prevalence varies, with intermediate prevalence in East Africa (e.g. Uganda) and high prevalence in Southern Africa (e.g. Zimbabwe) (UNAIDS and WHO, 2010).

In addition, those two areas (sub-Saharan and northern Africa) have two different HIV/AIDS prevalence trends: a decline in HIV/AIDS prevalence was observed in the sub-Saharan African countries studied in this thesis, both in Uganda (since the 1990s) and in Zimbabwe (since 1998) (UNAIDS and WHO, 2010), whereas an increase was observed in Algeria (since 2001) (Institut Pasteur d'Algérie, 2009), as has been observed in other MENA countries (UNAIDS, 2011). The decreasing rate in sub-Saharan Africa is a result of vigorous national prevention campaigns and the increasing availability of anti-retroviral therapy (UNAIDS and WHO, 2010). The increasing rate in Algeria probably reflects insufficient knowledge of HIV/AIDS in the population. In 2011, two surveys conducted among students in Algeria showed a very poor level of knowledge about HIV transmission methods (Abdennour, 2012b); (Abdennour, 2012a). Similar findings have been observed in other MENA countries (Boneberger et al., 2012); (Kobeissi et al., 2011); (Hassan and Wahsheh, 2011).

5.1.1 A view of Kaposi sarcoma epidemiology in Africa in the light of HIV/AIDS

With the emergence of the HIV/AIDS epidemic, KS incidence increased dramatically in the two sub-Saharan African populations studied (Uganda and Zimbabwe). The north–south geographical pattern of HIV/AIDS prevalence was reflected in the KS distribution, with higher rates in the sub-Saharan African populations than in the northern African populations (Algeria, Tunisia, and Egypt). Furthermore, the trend of KS incidence over time was also parallel to that of HIV/AIDS prevalence, as seen in Zimbabwe. These observations are consistent with the hypothesis that the geographical and temporal distributions of KS incidence in Africa follow those of HIV/AIDS prevalence.

There were, however, some exceptions. For example, in Uganda, although KS rates have fallen in young adult men (≤50 years old), in line with HIV/AIDS trends in youth (Stoneburner and Low-Beer, 2004), KS incidence has remained stable among women and elderly men (>50 years old) despite the decreasing prevalence of HIV/AIDS in those population subgroups (Stoneburner and Low-Beer, 2004). In addition, KS incidence rates in women in Zimbabwe and Uganda were similar despite a higher HIV/AIDS prevalence in women in Zimbabwe. Moreover, KS incidence was similar in men and women in Uganda and was higher in men than in women in Zimbabwe, although in both countries HIV/AIDS prevalence was higher in women than in men. These observations suggest the existence of at least one other co-factor (e.g. HHV-8) that may also influence the KS geographical patterns, time trends, and sex distribution in a population.

5.1.2 HIV/AIDS epidemiology in Algeria

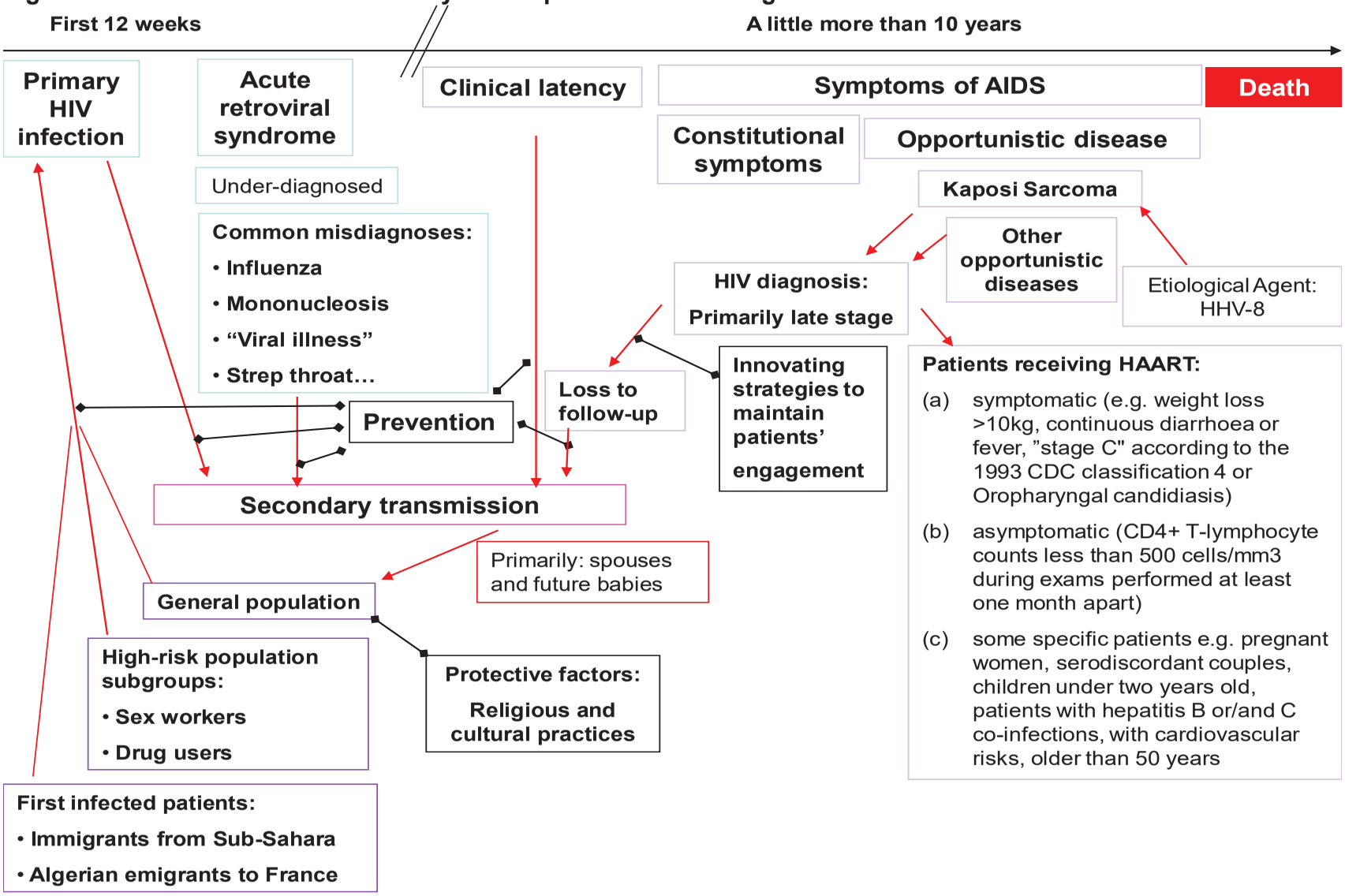
In Algeria, despite low rates of HIV/AIDS prevalence, I observed an increase in the number of diagnosed HIV/AIDS cases in the general population: 41 cases in the pre-HAART era (1988–1997) versus 115 during the HAART era (1998–2010). The increase in case numbers may be attributable, at least in part, to the implementation of surveys and the establishment of voluntary testing centres in the past decade, and it is difficult to tease out the impact of this on HIV/AIDS prevalence over time. The other reason for an increase in HIV/AIDS prevalence is a true increase in risk due to a poor knowledge of HIV/AIDS in the population (Abdennour, 2012a;Abdennour, 2012b).

At the beginning of the emergence of the HIV/AIDS epidemic in Algeria, cultural and religious habits served as effective protection against HIV infection (Abu-Raddad et al., 2010). Thus, HIV/AIDS cases were confined to immigrants from sub-Saharan Africa and Algerian emigrants to foreign countries, usually France (Figure 22). Over the years, this profile changed and the HIV/AIDS epidemic was observed mainly among Algerian sex workers and intravenous drug users (Touaibia et al., 2011). From this current work retrospectively studying the patterns observed in the general population, although HIV/AIDS was rare, an increased number of cases was observed in the general population (in men, women, and children). Even though I did not know for all patients whether they belonged to high-risk groups (e.g. sex workers or intravenous drug users), I observed during the study the increasing numbers of HIV-infected families. For example,

a man who used sex-worker services (before or during his marriage), or an intravenous drug user like the patient presented in the case report (Section 4.4), became HIV-positive and infected his wife, who infected her child by vertical transmission. At the infectious disease service of the CHU of Oran, I was informed that physicians organized family medical consultations, thereby showing an adaptation to the transition of the HIV/AIDS epidemic in Algeria. A physician from Algiers, the capital, confirmed that these consultations were also organized in the CHUs of Algiers. Algeria seems to be in a concerning and critical phase regarding the HIV/AIDS epidemic, and more effective prevention programmes may be needed to complement the current actions to fight HIV/AIDS.

Since 1998, HAART has been available free of charge in Algeria. Since then, the yearly risk of death among patients diagnosed with HIV/AIDS has declined, from 100% in 1998 to 8% in 2010, while the percentage of patients treated with HAART has increased, from 13% in 1998 to >80% after 2002. Although risk of death in HIV-positive patients has decreased since the introduction of HAART, SMRs did not continue to decline after 2006. In sub-Saharan Africa, SMRs varied between 553, for patients starting HAART with the worst prognosis, and 30, for patients starting HAART with the best prognosis. For those HIV-positive patients who survived the first year after starting HAART, SMRs continued to decrease during the second year, and after two years of HAART mortality reached that of the general population for those patients starting HAART with the best prognosis (Brinkhof et al., 2009). These observations suggest that if SMR remained high in HIV-positive patients in Algeria and did not decline after 2006, almost all of the patients who were treated were at the late stage of AIDS. At the end of the study, one third of all patients had been lost to follow-up, one third were alive, and one third had died. Of the patients who had died, 84% had died in the same year as, or in the year after, their HIV/AIDS diagnosis. This result also suggests that almost one third of patients diagnosed with HIV/AIDS in north-eastern Algeria before 2010 were at the late stage of the disease. The remarkable proportion of patients very probably diagnosed at the late stage of AIDS and the HIV-positive case report suggest that the medical system failed to detect HIV-positive patients at an earlier stage of the disease, which would prevent HIV transmission and would increase the life expectancy of HIV-positive patients; thus, these findings emphasize the need for earlier diagnosis of HIV in Algeria.

Figure 22: HIV infection natural history and Kaposi sarcoma in Algeria



5.1.3 NHL epidemiology in Africa

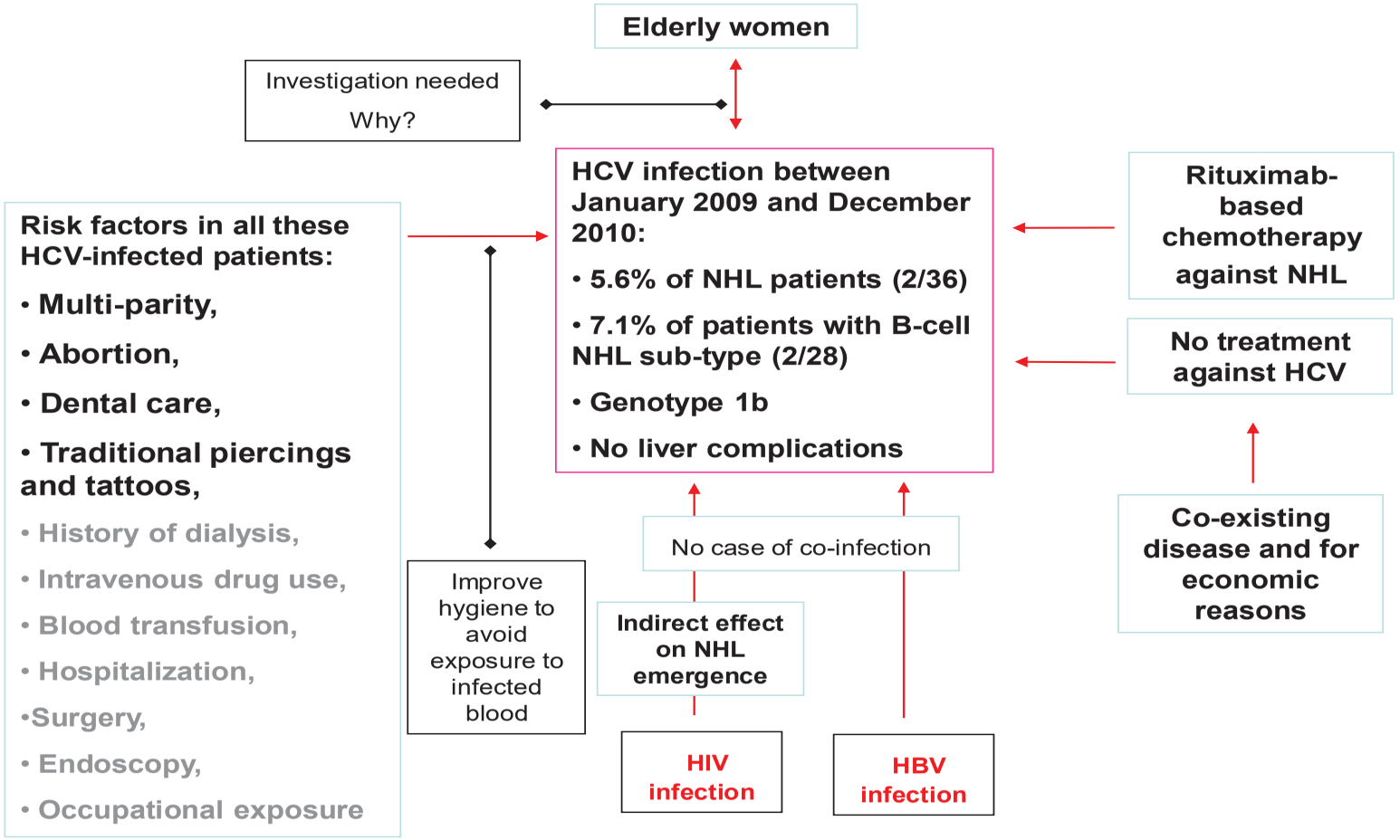
Among the five African populations studied in this thesis, namely Egypt, Tunisia, Algeria, Zimbabwe, and Uganda, incidence of NHL, which is an AIDS-related cancer, was the highest in both sexes in Egypt, where the reported HIV/AIDS prevalence was very low. Several etiological viruses are responsible as the cause of NHL. HCV infection, recently linked to NHL (Bouvard et al., 2009), may explain this observed pattern. HCV prevalence in Egypt was the highest worldwide (up to 20%) (Darwish et al., 1996), which has been related to national anti-schistosomal campaigns using parenteral therapy between the 1950s and the 1980s (Frank et al., 2000), whereas HCV prevalence in Zimbabwe and Uganda was 2.0% and 6.6%, respectively (Madhava et al., 2002). HCV prevalence in Egypt was the highest in elderly men (Cowgill et al., 2004), similar to the age pattern of NHL incidence.

In Algeria, another country with low HIV/AIDS prevalence, NHL incidence has increased since 1995 (Bouhidel et al., 2002;Bouhidel, 2007;Bouhidel, 2011). In the Batna region, the number of NHL patients diagnosed in the haematological service of the CHU of Batna, which is the only service in the region, almost tripled between 2009 and 2010, from 10 to 26 cases, without any changes in screening or care access. The prevalence of HCV infection was 5.6% (2/36) in these NHL patients and 7.1% (2/28) among those with B-cell NHL (Figure 23). This prevalence was higher than that estimated in the general population in Algeria (1–3%) (Sari, 2009).

In eastern Algeria (Batna region), HCV-positive patients with NHL were more likely to be elderly women with a high risk of nosocomial exposure to HCV (Figure 22). HCV infection may partly explain the emergence of NHL in Algeria, especially among patients with a high risk of nosocomial HCV infection.

NHL patients with HCV infection in the haematology service of the CHU of Annaba were treated with immunochemotherapy. several reports have shown that rituximab-based chemotherapy for NHL can increase HCV RNA levels and may aggravate hepatic lesions in onco-haematological patients, although the aggravation of hepatic lesions is less frequent and less severe than in HBV-infected subjects (Coppola et al., 2011); (Nooka et al., 2011). In the cases considered in this thesis, no patient treated with rituximab developed liver-related complications or exacerbation of the hepatitis. In addition, I observed that in the Annaba region, one third of the 98 NHL patients diagnosed

Figure 23: Disease pathway: Co-occurrence of B-cell non-Hodgkin lymphoma and chronic hepatitis C virus infection



between 2009 and 2010 were not tested for HCV and HBV infections. Therefore, I recommend systematic screening for HCV and HBV infections before starting chemotherapy and liver function assessment before and during NHL treatment.

5.1.4 Cervical cancer epidemiology in Africa

Cervical cancer was the most common cancer in females in four of the five populations studied (1998–2002) in this thesis (the exception was Gharbiah, Egypt). Cervical cancer incidence in Africa followed a north–south gradient, with 4.5-fold higher incidence in sub-Saharan Africa than in northern Africa. This reflects HIV/AIDS distribution in the continent, despite the fact that HIV/AIDS is only a mediating factor to HPV. HPV prevalence was 10.9% in northern Africa (10.5% in Algeria, 14.6% in Tunisia, and 10.3% in Egypt) and 33.6% in East Africa (WHO and ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre), 2010). Cervical cancer incidence in women >50 years old was higher in Zimbabwe than in Uganda, which may be explained by the higher prevalence of infection with more oncogenic HPV subtypes and by earlier sexual activity in Zimbabwe. The use of hormonal contraceptives is high and varies across the countries in northern Africa (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007), which probably explains the variation in cervical cancer incidence rates among northern African populations where HIV/AIDS prevalence was similar. Smoking prevalence is low (Pampel, 2008), and smoking rates may not be an important explanation for the variation in cervical cancer incidence rates among African women (see section 4.1).

5.2 Cancer registration: biases and limitations

5.2.1 Underestimation due to underdiagnosis

A small number of cancer cases might not be captured in the registration network. For example, some patients who live within the capture area of the registry may be diagnosed or treated in a hospital outside of the registry network. In Setif (Algeria), agreements have been made with the hospitals outside the registration area to notify the registry of any cancer cases among residents of the registration area. These outside hospitals are visited regularly to collect records, but some small underestimation is possible. Furthermore, because autopsy was not mandatory (with the exception of Bulawayo, Zimbabwe), some cancer cases may not have been detected. For example, among the Algerian patients

who were diagnosed at the late stage of HIV/AIDS and who died rapidly, some cancers may not have been diagnosed. Therefore, cancer incidence may be underestimated. As another example, in Gharbiah such underestimation may also occur and most likely occurs among elderly people in rural areas.

5.2.2 Data quality

Despite the use of the best available African cancer data, the data quality from these registries was limited. Compared with the other registries, the Harare Cancer Registry (Zimbabwe) had the lowest histological verification (56% for KS, 72% for cervical cancer, and 82% for NHL). In Harare (Zimbabwe) and in Kyadondo County (Uganda), the percentage of MV was less than that expected in Africa (Parkin et al., 2003), which is a potential indicator of poor data validity in these cancer registries. For the geographical comparison, I compared data from registries in northern African with 100% of MV cases with those from the two above-mentioned registries in sub-Saharan Africa. This means that I compared cases that I am sure were cancers with cases for some of which I am not sure that they were really cancers. Rates for sub-Saharan African populations were probably overestimated, and the north–south difference may in fact be smaller than what I found. In addition, the percentage of DCO cases (i.e. 12%) observed in Harare shows that there were a number of cancer cases with no information on the methods used to diagnose these cases; this also indicates poor data validity (Abu-Raddad et al., 2010). In the current thesis, data from Harare were compared with those from Bulawayo (both in Zimbabwe); however, the data quality seemed to be better for the data from Bulawayo. Death certification before burial was mandatory in Bulawayo, and the bodies of all people who died outside a hospital in the African townships of the city were brought to the mortuary for autopsy before certification. The high autopsy rate is in part responsible for the very high rate of histological proof of diagnosis in Bulawayo (82.8%) (Skinner et al., 1993). The increase in rates observed with the emergence of the HIV/AIDS epidemic may not in fact be as high as observed in Zimbabwe. Comparison of cancer rates using data of different qualities may introduce bias in the conclusions presented in this thesis.

Even if the data quality did not reach that of registries in Europe or North America, description and analysis of the cancer epidemiology can be carried out and interpreted with caution. At the moment, the African cancer registries are the main source of

population-based data and provide highly important input for understanding the public health problems that affect this continent, and how to combat them.

5.3 HIV/AIDS and HCV data extraction: biases and limitations

The retrospective study on HIV/AIDS burden in north-eastern Algeria and HCV burden in eastern Algeria was affected by some missing information at various levels.

5.3.1 Incompleteness of data

During the retrospective study performed in Algeria, incompleteness of data for salient etiological, predictive, and/or prognostic factors in HIV/AIDS and NHL patient records was often encountered during data collection for this thesis. For example, some important variables like CD4 count were not found in all records. In addition to economic limitations hampering complete blood work, this can be explained by the fact that many patients were diagnosed at the late stage of HIV/AIDS and therefore died before all exams had been completed. If CD4 count were available for all patients, patients could be stratified into two categories according to CD4 cell count at first presentation for diagnosis: patients with CD4 ≤ 200 cells/mm3 and patients with CD4 >200 cells/mm3. Multivariate logistic regression could be performed to assess the risk factors associated with first presentation for care of patients with CD4 count ≤ 200 cells/mm3. Independent variables that could have been identified were older age, male gender, route of HIV transmission, migrant populations, and geographical areas (wilayas). Data on the date of death and the last date on which the patient was seen before dropping out of regular care would allow survival analysis with Cox regression model to assess whether HIV-infected patients who came to the health care system with CD4 count ≤ 200 cells/mm3 had higher mortality. The risk factors identified to be associated with late presentation could be used in formulating targeted public health interventions to improve early HIV diagnosis.

5.3.2 High proportion of loss to follow up

The relatively high percentage of loss to follow-up among the patients with HIV/AIDS included in the retrospective study of this thesis (Section 4.3) may have introduced further bias. The number of prevalent cases may have been underestimated. These patients lost to follow-up may be either patients with very poor health who preferred to die at home or healthy seropositive persons who refused to be followed up or treated because of

prevailing social stigma, denial of illness, and/or unconsciousness of disease severity. Further study is needed to assess the actual extent to which HIV-diagnosed patients attending the infectious disease service of the CHU of Annaba died, were lost to follow-up, or attended outpatient services intermittently. Innovative strategies are needed to identify those who are most likely to drop out of regular care.

5.3.3 Too-large area coverage of infectious disease and haematological services in each Algerian region

The haematology service of the CHU of Batna is the only such facility in the eastern region of Algeria, covering an area with nine wilayas (6 953 209 inhabitants). However, although they are referred to the Batna service centre, NHL patients living far from the service centre may prefer to go to Algiers for care. Similarly, the infectious disease service of the CHU of Annaba is the only STI/HIV/AIDS reference centre in the north-eastern region, covering an area of six wilayas (2 837 150 inhabitants). Virtually all HIV/AIDS patients living in this area are referred to, treated, and followed up in the infectious disease service of Annaba. However, some patients may not go to the centre because of the long distance to the care facility and therefore would not be included in the study. Thus, the current cases reported in this study may well be only the tip of the iceberg.

Generally, limited access to health care could be a reason for underestimation of HIV/AIDS prevalence all over Algeria. The seven STI/HIV/AIDS reference centres were distributed according to regional population size and not according to the most affected regions. The eastern and central regions are the most populous (11 399 580 and 8 804 198 inhabitants, respectively; 67% of the national population in 2008) (Office National des Statistiques, 2012) and have five of the seven STI/HIV/AIDS reference centres — in the cities of Annaba, Constantine, and Setif for the eastern region, and two in the capital, Algiers, for the central region. However, in 2001–2008, 6% of HIV-positive diagnosed patients were from the eastern region, whereas 55.4% were from the western and southern regions (Institut Pasteur d'Algérie, 2009). In the southern region, the wilaya furthest from Tamanrasset, where the STI/HIV/AIDS reference centre of the southern region is located, is Tindouf. The distance by road between Tindouf and Tamanrasset is about 2200 km. The STI/HIV/AIDS reference centre of Oran is the closest centre to Tindouf, but the distance between these two wilayas is 1470 km. Tindouf municipality is

close to the Moroccan and Mauritanian borders (50 km and 65 km away, respectively), and it is a major hub for illegal immigration from sub-Saharan Africa to Europe (Spiga, 2005). Between 1985 and 2008, one case from Tindouf wilaya was reported by the Pasteur Institute of Algiers, Algeria. This count may be underestimated because of limited access to health care. This example demonstrates that the number of HIV/AIDS cases detected in the western and southern regions may be underestimated more than those in the eastern region, where the main work of this thesis was carried out. Public health officials should consider increasing the number of STI/HIV/AIDS reference centres in areas where HIV/AIDS rates may be high.

5.4 Public health interest of the thesis work performed

5.4.1 Successful HIV/AIDS control in Sub-Saharan Africa by prevention programmes

In sub-Saharan populations such as Uganda and Zimbabwe, the HIV/AIDS epidemic seems to have been controlled and prevalence rates have gone down. These sub-Saharan African countries have had success in combating the HIV/AIDS epidemic using campaign that encouraged people to abstain, be faithful, and use condom – the ABC campaign(Stoneburner and Low-Beer, 2004;Gregson et al., 2006). Further to effective prevention programmes, antiretroviral therapy coverage has been scaled up, which may be the main keys to this success (Green et al., 2006); (Halperin et al., 2011). These changes in the HIV/AIDS epidemic are partly reflected in the geographical patterns and the time trends of KS, the most common cancer among HIV/AIDS patients. Thus, the war against HIV/AIDS seems to have also benefited the war against KS. This success in decreasing the rate of KS incidence should be widely heralded. Therefore, HIV/AIDS prevention and management strategies in Uganda and Zimbabwe are moving in the right direction, and should be maintained and replicated in other African countries that present a similar pattern of HIV/AIDS and KS incidence.

5.4.2 Increasing awareness among health care providers and sexual education among the general population in Algeria

The most common transmission route of HIV/AIDS in Algeria has been through heterosexual intercourse (Touaibia et al., 2011). Due to low awareness, poor knowledge

of sexual disease, and social taboos, horizontal infection transmission through sexual contact has brought HIV/AIDS into families, and it has then spread to the younger generation through vertical transmission (mother-to-baby) (see Sections 4.3 and 4.4). To reduce the transmission of the disease, prevention programmes should increase free screening among high-risk groups and encourage people to abstain, be faithful, and use condoms – the ABC campaign which succeeded in combating the HIV/AIDS epidemic in the sub-Saharan African countries studied. However, provision of free condoms could be interpreted as encouraging sexual promiscuity, hence causing some reluctance to adopt this contraception to prevent transmission of STIs. Some Algerian attached to their religious or cultural traditions, might prefer campaigns encouraging only abstinence and faithfulness. Thus, these prevention programmes should be run in parallel with improved education on HIV/AIDS (including the severity of this incurable disease) to realize that condom use by people who could not be abstinent or faithful is a real requirement. Prevention programmes should focus on avoiding the further spread of HIV/AIDS to the general population.

Almost one third of HIV-positive patients seemed to be diagnosed at the late stage of AIDS (see Sections 4.3 and 4.4). Therefore, educating the high-risk population and health care providers to increase awareness on key signs and symptoms of HIV/AIDS may lead to earlier detection of the disease. Early detection will not only reduce mortality but also reduce wider transmission of the disease.

5.4.3 Prevention of non-Hodgkin lymphoma by decreasing HCV infection rates through reduction of nosocomial infection

HCV seemed to contribute to the emergence of NHL in Africa (see Sections 4.4 and 4.5). In Algeria, one of the transmission routes of HCV seems to be hospital-acquired (nosocomial) infection. Although HCV prevalence among NHL patients is lower than that observed in Egypt (1–3% vs 20%, respectively), this nosocomial HCV infection is an unfortunate event which can easily be prevented through improved hygiene in hospitals and medical centers by avoiding the re-use of needles, the correct sterilization of dental instruments and the systematic serological test for HCV before blood donation.

5.4.4 Reducing cervical cancer incidence in Africa by using an appropriate screening test and vaccination

In developed countries, the main strategy that has been responsible for the reduction of the incidence of invasive cervical cancer is effective screening programmes that allow the early detection and treatment of precancerous lesions. Of the 275 000 women who die from cervical cancer every year, 88% live in developing countries (Ferlay et al., 2010). However, such screening programmes were non-existent in Uganda and Egypt, and the estimated coverage of cervical cancer screening was low in all the populations studied in this thesis. Visual screening and treatment services are sustainable and effective ways of improving the provision of cervical cancer control by health services in African countries (Teguete et al., 2012;Muwonge et al., 2010;Ngoma et al., 2010;Sankaranarayanan et al., 2004). With appropriate training, monitoring, continuing practice, and quality assurance, adequate standards of colposcopy can be attained in sub-Saharan Africa (Muwonge et al., 2009). Public health decision makers should increase implementation of an accurate, easy-to-apply, simple, inexpensive, culturally acceptable, and safe screening test to further decrease the burden of cervical cancer in Africa.

In recent decades, routine screening programmes have reduced cervical cancer morbidity and mortality in high-income countries, and this trend is expected to accelerate as vaccination coverage is scaled up (WHO, 2008). Two HPV vaccines were approved by WHO in 2006 and have been available through routine immunization in more developed countries since 2007. The high cost of the vaccine and the challenges of immunizing girls 9–13 years old have been barriers to introduction in developing countries (Markowitz et al., 2012). A 5-year delay in introducing the HPV vaccine to developing countries would result in 1.5–2 million preventable deaths (Ferlay et al., 2010). Rwanda was the first African country to implement national immunization after receiving vaccine through donation programs in 2011 (Markowitz et al., 2012). Rwanda's HPV vaccination programme achieved 93% coverage after the first three-dose course of vaccination among girls in grade six. Rwanda's example should motivate other African countries to explore universal HPV vaccine coverage, although implementation must be tailored to the local context (Binagwaho et al., 2012). On World Cancer Day 2013, the Global Alliance for Vaccines and Immunisation (GAVI) announced the first African countries to receive GAVI support for HPV vaccines through demonstration programmes: Ghana, Kenya,

Madagascar, Malawi, Niger, Sierra Leone, and Tanzania (GAVI Alliance, 2013). This introduction of HPV vaccine in Africa is the start of a global effort to protect all girls against cervical cancer.

5.5 Public health perspectives of the thesis work performed

5.5.1 Studying temporal and geographical patterns of Kaposi sarcoma incidence for insight into the role of HHV-8

KS incidence has remained stable in Ugandan women and men >50 years old. This Ugandan KS pattern suggests that in this country HIV/AIDS is not the only main cause of KS spread; other factors, such as HHV-8 infection, might be involved and should be taken into account in public health strategies to limit the spread of KS. Furthermore, studies aiming to evaluate differences between men and women, and between young and elderly men, should be carried out in Uganda. These studies will provide a better understanding of HHV-8 transmission and thus enable the implementation of prevention programmes and better KS patient care.

5.5.2 Integration of social and cultural perspectives into epidemiological studies to improve HIV/AIDS control

Religious habits and social pressure play a large role in limiting the spread of STIs such as HIV/AIDS in the MENA countries. For several decades these factors were indirectly protective against STIs through abstinence, monogamy, and circumcision (Abu-Raddad et al., 2010). However, now with modernization STI prevalence has increased, and taboos and social pressure have hampered sexual education and the development of prevention campaigns to improve HIV/AIDS control and patient management. Integrating sociological theories in studying disease, i.e. HIV/AIDS perception and transmission in Algeria, could lead to the establishment of better management protocols and, eventually, improved disease control in such countries.

5.5.3 HCV genotyping in Algeria

Hepatitis C virus (HCV) infection is a major global public health issue. It is estimated that the global prevalence of HCV infection is approximately 2.8% (or 180 million people)

(Lavanchy, 2011; Mohd et al., 2012). HCV has a high viral heterogeneity. According to the nucleotide divergence, there are at least six genotypes, each of them containing a series of subtypes (Kuiken and Simmonds, 2009). HCV genotypes have a strikingly different geographical and epidemiological distribution, and genotype identification is clinically important to tailor the dosage and duration of the treatment, because a different pattern of treatment response and, consequently, a distinct therapeutic approach is required for each genotype (Sy and Jamal, 2006). In several areas of the world, HCV genotype 1 is reported as the most common infecting genotype among chronically infected patients. HCV genotypes 1, 2, and 3 appear to have a worldwide distribution, and their relative prevalence varies from one geographical area to another (Shepard et al., 2005). HCV subtypes 1a and 1b are the most common genotypes in the USA (Germer et al., 2011) and in Europe (Cornberg et al., 2011). The predominant subtype reported in Japan is subtype 1b, which is responsible for up to 73% of cases of HCV infection (Sievert et al., 2011). HCV subtypes 2a and 2b are relatively common in North America, Europe, and Japan, and subtype 2c is commonly found in northern Italy (Germer et al., 2011; Cornberg et al., 2011). HCV genotype 4 appears to be prevalent in North Africa and the Middle East (Kamal and Nasser, 2008), and genotypes 5 and 6 seem to be confined to South Africa and south-eastern Asia, respectively (Chamberlain et al., 1997). The northern African data are based on the information from Egypt, Libya, Tunisia, and Morocco only. However, there have been no published studies on the prevalence of HCV genotypes in Algeria (Daw and Dau, 2012). Only one poster was presented, by Benabdellah and colleagues, in 2012 at the 15th Annual Meeting of the European Society for Clinical Virology in Madrid (Benabdellah et al., 2012). In this retrospective study, they investigated HCV genotypes in 140 patients from Oran (north-western Algeria) between 2005 and 2011. The genotype 2a/2c was predominant (47%).

I was involved in a retrospective study aiming to identify the prevalence of different HCV genotypes in eastern Algeria and to assess the correlation between the HCV genotypes and the demographic profile. The original article entitled “Hepatitis C virus genotypes in eastern Algeria: a retrospective study” was accepted by *World Journal of Hepatology* in March 2013.

5.5.4 Non-infection-related cancer in Africa

Exploring epidemiological transitions in low-income countries, particularly in Africa, may be the next step of my research work. Although a substantial proportion of the cancer burden in Africa is attributable to infections (e.g. HIV, HPV, HCV), there has been a dramatic increase in recent years in the incidence of non-infection-related cancers due to changes in the environment, changes in the occupational sector, and the adoption of western lifestyles as a consequence of economic development and urbanization. Research programmes on the causes of non-infection-related cancers in Africa may be set up.

For example, an epidemiological study on cancer and obesity in Algeria could be carried out. According to the Global Burden of Disease study, there was a general increase in healthy life expectancy at birth in men and women in Algeria between 1990 and 2010 (from 59 to 62 in men and 60 to 63 women) (Salomon et al., 2013). In 2011, Algeria was for the first time ranked among the “high human development” countries. The human development index for Algeria has increased since 1980, from 0.454 in 1980 to 0.551 in 1990 and 0.698 in 2011 (UNDP, 2012). Alongside these improvements in life expectancy, education, and income, Algeria has entered a phase of epidemiological transition marked by the persistence of communicable diseases characterizing developing countries (infectious diseases of children, tuberculosis, waterborne, zoonoses) and the emergence of non-communicable diseases (cancer, diabetes, cardiovascular, renal, neurological, and respiratory diseases), which are taking an increasingly important place in the burden of disease. In the context of the TAHINA project (Transition and Health Impact in North Africa) financed by the European Union, the Algerian National Institute of Public Health (INSP) carried out a national survey aiming to analyse the causes of death in Algeria in 2002. According to the Global Burden of Disease classification, non-communicable diseases (NCDs) were the second most common cause of death in Algeria. In the overall distribution of deaths according to the International Classification of Diseases – Tenth Revision (ICD-10), the third leading cause of death was cancer (9.5% of all deaths). In the group of NCDs, cardiovascular disease ranked first as cause of death, with 44.5% of deaths, followed by malignant tumours, with 16.0% of deaths (Ait Mohand et al., 2008). Another national survey was conducted by the INSP in the context of the TAHINA project in 2005, aiming to describe overweight and obesity according to epidemiological

characteristics in adults >30 years old. This survey showed that 21% of Algerian adults (30% of women and 9% of men) were obese and that 56% of the population was overweight (67% of women and 41% of men) (Atek et al., 2010).

Increased body mass index is associated with an increased risk of cancers of the oesophagus, pancreas, colorectum, gallbladder, breast, endometrium, and kidney (WHO, 2012). Cancer epidemiological studies may be performed aiming to analyse how high frequencies of overweight and obesity, especially in women, have affected cancer incidence rates in Algeria. These studies will contribute to the provision of a picture of obesity-related cancer epidemiology in Algeria, which can be used to design strategies and policies for improving obesity prevention, cancer patient care, and allocation of national resources.

Conclusion

The impact of HIV and HCV infection on cancer burden is a wide subject that would need several thesis works to explore. This thesis emphasizes the need to encourage and develop effective prevention programmes against viral infections as the main strategy to prevent virus-related cancers. Thus, cancer prevention could be included in larger public health actions.

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1 **Chaabna K**, Boniol M*, De Vuyst H, Vanhems P, De Ávila Vitoria MA, Curado MP. Geographical Patterns of Kaposi Sarcoma, Non-Hodgkin Lymphomas and Cervical Cancer Associated with HIV Infection in Five African Populations. European Journal of Cancer Prevention. 2012 Jan;21(1):1-9. PMID:21955799.

2 **Chaabna K***, Soerjomataram I, Rouabhia S, Chichoune S, Scholtes C, Vanhems P, Saidi M, Forman D. Co-occurrence of Diffuse Large B Cell Non-Hodgkin Lymphoma and Chronic Hepatitis C in Algerian Patients: Two Case Reports. Accepted by Journal of Cancer Research and Therapeutics in 09/2012 **(*Corresponding author)**

3 **Chaabna K***, Bray F, Wabinga HR, Chokunonga E, Borok M, Vanhems P, Forman D, Soerjomataram I. Kaposi sarcoma trends in Uganda and Zimbabwe: a sustained decline in incidence? International Journal of Cancer (2013). PMID: 23436712 **(*Corresponding author)**

4 **Chaabna K*,** Boudiaf Z, Vanhems P, Rouabhia S, Laouar M, Soerjomataram I. Very late presentation of HIV/AIDS in Algeria: a need of increase awareness and early detection. (Submitted) **(*Corresponding author)**

5 Rouabhia S, Sadelaoud M, **Chaabna K**, Toumi W, Abenavoli L. Hepatitis C virus genotypes in eastern Algeria: a retrospective study. Accepted by World Journal of Hepatology in 03/2013.

6 **Chaabna K**, Newton R, Vanhems P, Laouar M, Forman D, Soerjomataram I. All-cause mortality in HIV-positive patients from six Algerian regions before and during HAART era. In preparation (Planned submission April 2013).

7 **Chaabna K**, Soerjomataram I, Vanhems P, Forman D, Bouzeghoub S. HIV/AIDS national and regional trend and patient profile in Algeria from 1985 to 2008. In preparation (Planned submission May 2013).

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1 **Chaabna K**, Soerjomataram I, Bray F, Wabinga HR, Chokunonga E, Borok M, Vanhems P, Forman D. Trends in HIV prevalence and Kaposi sarcoma incidence in Africa. *48th IARC scientific council, Lyon, France, January 2012.* (**Poster**)

2 Chaabna K, Bray F, Wabinga H, Chokunonga E, Vanhems P, Forman D. SP3-67 Kaposi sarcoma incidence in Uganda and Zimbabwe, before and during HIV/AIDS epidemic. ***IEA World Congress of Epidemiology*****,** August 2011, Edinburgh, Scotland. ***Journal of Epidemiology and Community Health*** [J. Epidemiol. Community Health]. Vol. 65, Suppl., pp. A426-A427. 2011. *(**Published Abstract**)*

3 **Chaabn K**, Bray F, Wabinga HR, Chokunonga E, Borok M, Vanhems P, Forman D. Kaposi sarcoma incidence in Uganda and Zimbabwe before and during the HIV/AIDS epidemic. *GRELL meeting, Caen, France, June 2011. (***Oral presentation**)

4 **Chaabna K**, Boniol M, De Vuyst H, Vanhems P, De Ávila Vitoria MA, Curado MP. Distribution Géographique du Sarcome de Kaposi, du Lymphome Non-Hodgkinien et du cancer du col de l'utérus associés à l'infection au VIH, dans cinq populations africaines en 1998-2002. *Vth National Days of Infectious Disease Prevention, Oran, Algeria, May 2011.* (**Oral presentation**)

5 **Chaabna K**, Bray F, Wabinga HR, Chokunonga E, Borok M, Vanhems P, Forman D. Incidence du sarcome de Kaposi en Ouganda et au Zimbabwe avant et au cours de l'épidémie de VIH**.** *Vth National Days of Infectious Disease Prevention, Oran, Algeria, May 2011* (**Oral presentation**)

6 **Chaabna K**, Boniol M, De Vuyst H, Vanhems P, De Ávila Vitoria MA, Curado MP. Geographical patterns of Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer associated with HIV infection in five African populations. *6th Cancer Scientific Forum of the Cancerpôle CLARA, Lyon, France, March 2011.* (**Poster**)

7 **Chaabna K**, Bray F, Wabinga HR, Chokunonga E, Borok M, Vanhems P, Forman D. Kaposi sarcoma incidence in Uganda and Zimbabwe, before and during HIV/AIDS epidemic. *47th IARC scientific council, Lyon, France, January 2011.* (**Poster**)

8 **Chaabna K**, Boniol M, De Vuyst H, Vanhems P, De Ávila Vitoria MA, Curado MP. Geographical patterns of Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer associated with HIV infection in five African populations. *Scientific BMIC Graduate School Days, Lyon, France, November 2010.* (**Oral presentation**)

9 **Chaabna K**, Boniol M, De Vuyst H, Vanhems P, De Ávila Vitoria MA, Curado MP. Distribution Géographique du Sarcome de Kaposi, du Lymphome Non-Hodgkinien et du cancer du col de l'utérus associes a l'infection au VIH, dans cinq populations africaine en 1998-2002. *IVth International Congress of Epidemiology «Du Nord au Sud» by ADELF (Association des Epidémiologistes de Langue Française), Marseille, France, September 2010.* (**Oral presentation**)

10 **Chaabna K**, Boniol M, De Vuyst H, Vanhems P, De Ávila Vitoria MA, Curado MP. Distribution Géographique du Sarcome de Kaposi, du Lymphome Non-Hodgkinien et du cancer du col de l'utérus associes a l'infection au VIH, dans cinq populations africaine en 1998-2002. *IVth International Congress of Epidemiology «Du Nord au Sud» /* ***Revue d'Épidémiologie et de Sante Publique*** *58S (2010) S51-S98. (****Published Abstract****)*

Annex

Annex 1

Questionnaire 1 : Description de la prévalence du VIH et des hepatitis C et B chez les patients avec lymphome en Algérie.

Nom :..... Prénom :.....

Date de naissance : /__ //__ / /__ //__ / /__ //__ //__ //__ /

Age : /__ //__ / Sexe (M/F) : /__ /

Nº de dossier : /__ //__ //__ //__ //__ //__ //__ //__ //__ //__ /

Adresse (wilaya) : .....

Diagnostic du lymphome :

Hodgkin ☐ Non-Hodgkin ☐

Si LNH, typologie :.....

Date de diagnostic du cancer : /__ //__ //__ //__ //__ //__ //__ //__ /

Tests Biologiques :

VIH :

Anti HIV : Positif ☐ Négatif ☐

Date de diagnostic du VIH : /__ //__ / /__ //__ / /__ //__ //__ //__ /

Charge virale VIH :.....Copies/ml

HCV :

Anti HCV : Positif ☐ Négatif ☐

Si positif, charge virale HCV :.....Copies/ml

Génotype :.....

Date de diagnostic du HCV : /__ //__ //__ //__ //__ //__ //__ //__ /

HBV :

Anti HBs : Positif ☐ Négatif ☐

Si positif, charge virale HCV :.....Copies/ml

Anti HBc Ig M : Positif ☐ Négatif ☐

Anti HBc Ig G : Positif ☐ Négatif ☐

Date de diagnostic du HBV : /__ //__ / /__ //__ / /__ //__ //__ //__ /

Statut :

Vivant ☐ Décédé ☐ Perdu de Vue ☐

Date du décès ou de dernière nouvelle : /__ //__ //__ //__ //__ //__ //__ //__ /

Annex 2

Questionnaire 2 : Facteur de Risque d'hépatite virale chronique et VIH

Nom :..... Prénom :.....

Date de naissance : /__ //__ / /__ //__ / /__ //__ //__ //__ /
Age : /__ //__ / Sexe (M/F) : /__ / Adresse (wilaya): .....

Nº de dossier : /__ //__ //__ //__ //__ //__ //__ //__ //__ //__ /

Facteurs de Risque	OUI	NON
Soin dentaire		
Transfusion		
Accouchement		
Avortement		
Hospitalisation		
Chirugie		
Endoscopie		
Dialyse		
Piercing		
Tatouage		
Exposition Professionnelle		
Toxicomanie IV		
Rapport sexuel non protégé		
Prostitution		
Autre:.....		

Annex 3

Questionnaire 3 : Cancer chez les personnes infectées par le VIH en Afrique du nord (Algérie)

Nom :..... Prénom :.....

Date de naissance : /__ //__ / /__ //__ / /__ //__ //__ //__ /

Age : /__ //__ / Sexe (M/F) : /__ /

Nº de dossier : /__ //__ //__ //__ //__ //__ //__ //__ //__ //__ /
Adresse (wilaya) : .....

Tests Biologiques :

VIH :
Date de diagnostic du VIH : /__ //__ / /__ //__ / /__ //__ //__ //__ /

Charge virale VIH :.....Copies/ml
HCV :
Anti HCV : Positif ☐ Négatif ☐

Si positif, charge virale HCV :.....Copies/ml

Génotype :.....

Date de diagnostic du HCV : /__ //__ //__ //__ //__ //__ //__ //__ /
HBV :
Anti HBs : Positif ☐ Négatif ☐

Si positif,

Anti HBc Ig M : Positif ☐ Négatif ☐
Anti HBc Ig G : Positif ☐ Négatif ☐

Date de diagnostic du HBV : /__ //__ / /__ //__ / /__ //__ //__ //__ /

Diagnostic du Cancer :
Présence d'un cancer : Oui ☐ Non ☐
Si oui, typologie :.....
Date de diagnostic du cancer : /__ //__ //__ //__ //__ //__ //__ //__ /

Statut :
Vivant ☐ Décédé ☐ Perdu de Vue ☐
Date du décès ou de dernière nouvelle : /__ //__ //__ //__ //__ //__ //__ //__ /