The epidemiology of HPV and HIV among high-risk women and steady couples in Kigali, Rwanda
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CHAPTER 1

General introduction
GENERAL INTRODUCTION

This introduction will provide a brief historical and epidemiological overview of the human papillomavirus (HPV) and the human immunodeficiency virus (HIV). This will be followed by a description of the research setting in Rwanda where the data were collected, including a description of the different studies. Finally, an outline of the thesis is provided.

HPV: From Rigoni-Stern to Harald zur Hausen

The Italian surgeon Rigoni-Stern is quoted by many as the first to notice, in the early 19th century, that cervical cancer was rare among virgins and nuns in contrast to married women and widows.5 Although several of his contemporaries had also highlighted the link between sexual behavior characteristics and cervical cancer, Rigoni-Stern’s study was allegedly the first published epidemiological study using data from cancer registries.2,3 The notion that sexual behavior is linked with the development of cervical cancer has thus been around for 170 years. The hypothesis that a sexually transmitted pathogen is causal in the development of cervical cancer originates in the mid 20th century. In 1967 Martin et al wrote that “accepting the [...] observations [also portrayed in figure 1] as indicative of the epidemiologic importance of unstable sexual relationships among both men and women, [...] , it is proposed that squamous-cell cervical carcinoma shares many characteristics in common with communicable diseases that follow a venereal mode of transmission”.4 Several causative sexually transmitted infections (STIs) were considered, especially herpes simplex type 2 (HSV-2), and it was only in the 1980s that Harald zur Hausen identified HPV as the virus causing cervical carcinoma.5

![Figure 1: Model of factors associated with cervical cancer](image)

HIV: From ‘Patient 1’ to the discovery of HIV

The 1980s were important years in the history of HIV/AIDS as well. The first case of what was soon after called acquired immunodeficiency syndrome was described by the Centers for Disease Control (CDC) in 1981.6 Several theories regarding the etiological agents were hypothesized including viruses (i.e. cytomegalovirus), recreational drug abuse, semen overload and immune overload due to multiple infections.7 A report in 1982 by the CDC of a cluster of sexually related AIDS patients among homosexual men was among the first epidemiological investigations suggesting a role for a sexually transmissible agent.8 The hypothesis was then born that a retrovirus would be the etiological agent. The group of Robert Gallo had developed a method to grow T-cells in the mid-seventies, which allowed for the isolation of retroviruses.9 In the period 1983-1984 three different groups isolated retroviruses from patients with AIDS or at risk for AIDS: Francoise Barré-Sinoussi and Luc Montagnier isolated a virus they called the lymphadenopathy-associated virus (LAV) 10;
Robert Gallo’s group called their isolate the human T-lymphotropic virus type III (HTLV-III), which was later found to be identical to LAV and originated from the same source; whereas Jay Levy called his isolate the AIDS-associated retrovirus (ARV). It was not possible to propagate the virus in T-cell cultures, because the agent invariably killed the cells it infected. But when Popovic and others developed immortalized T-cell clones it became possible to propagate enough virus for detailed characterization. LAV and HTLV-III were found to be similar and the consensus name HIV was chosen. Within three years following the description of the first cases of AIDS the causal virus had thus been identified.

**HPV and HIV: A Nobel Prize gathering**

The causal viruses of cervical cancer and AIDS were thus identified around the same time. The history of both viruses coincided again in 2008 when the Nobel Prize was awarded to Françoise Barré-Sinoussi and Luc Montagnier for their work in the discovery of the causal role of HIV in the development of AIDS, and to Harald zur Hausen for his discovery that HPV was causative in the development of cervical cancer.

**GLOBAL HPV PREVALENCE RATES**

**HPV**

HPV is the most prevalent sexually transmitted infection (STI) worldwide. Up to 80% of women will at some point in their life have an HPV infection. The majority of infections are cleared though and only a minority becomes persistent. These persisting infections are at risk for progression to cervical (pre-) cancerous lesions. HPV prevalence varies per geographical area and age group; the highest prevalence is among young women soon after sexual debut living in East Africa. Global age-adjusted HPV prevalence was recently estimated at 11.7%, but prevalence is up to 33.6% in East Africa.

*Figure 2: Prevalence (left; UNAIDS 2009[22]) and prevalence of HPV among women with normal cytology (right, WHO information center[24])*
HIV

In 2009, an estimated 33.3 million people were living with HIV, with up to 70% of cases occurring in sub-Saharan Africa (22.5 million).22 Women in sub-Saharan Africa are disproportionately affected compared to men, with approximately 60% of infections occurring in women. HIV incidence in sub-Saharan Africa has declined to 1.8 million new infections in 2009, compared to 2.2 million new infections in 2001. Since the introduction of antiretroviral therapy, AIDS-related mortality rates have declined.23

The interplay between HPV and HIV

HPV incidence, prevalence and persistence are increased among HIV infected persons, also after taking sexual risk behavior into account.24,25 The biological explanation is that disruption of tight junctions in the mucosal epithelium by HPV-related proteins facilitates access to the basal cell layer, the target cells for HPV. Furthermore, the immunodeficiency reduces the clearance of established HPV infections. Moreover several recent articles reported on the increased risk of HIV acquisition among high risk (HR-) HPV positive persons. Especially HPV clearance appears to be associated with HIV acquisition. The possible biological explanation is that HPV clearance is mediated through a cellular immune response and leads to an increase in macrophages and T-cells, target cells for HIV.25,26

RESEARCH SETTING

Rwanda

Rwanda is a small, low-income country in East Africa. With a population of 10 million people, the country has the highest population density in Africa (373 persons per km²).26 Life expectancy at birth is 54 years for women and 50 years for men.27 Fertility rate is 5.5 per woman.28

Cervical cancer is the most common cancer among women in Rwanda, with an age-standardized incidence rate of 34.5 per 100,000 women per year.29 Each year, close to 1,000 Rwandan women are diagnosed with cervical cancer and almost 700 Rwandan women die of cervical cancer.30 Currently there is no organized cervical cancer screening program available in Rwanda. The Rwandan government has prepared a comprehensive five year cervical cancer prevention program, including HPV vaccination for young girls and screen-and-treat facilities for women over 35 years of age. The program is currently in the final preparatory stages before being rolled out.

A national HIV prevalence survey conducted in 2005 reported a 3.0% HIV prevalence among the general adult population (aged 15-49 years) in Rwanda.31 HIV prevalence varied per region, age and gender and was highest in Kigali where 8.0% of women and 5.2% of men were infected with HIV.
HIV prevalence was highest among women aged 35-39 years (6.9%) and among men aged 40-44 years (7.1%). In 2003, 44 health facilities were offering voluntary counseling and testing (VCT) services. In 2009 this had increased to 395 VCT sites. During the same period there was also a rapid increase in the number of health facilities offering combination antiretroviral therapy (cART) – from only 4 in 2002 to 269 in 2009. The number of people receiving cART has increased impressively from 870 in 2002 to 76,726 in 2009, with 77% of adults in need of cART receiving treatment. It is relevant to note that CD4 eligibility criteria for cART initiation changed over time from lower than 250 cells/ml to lower than 350 cells/ml since 2007.

Projet Ubuzima

Projet Ubuzima (PU) is an international, non-governmental organization in Kigali, Rwanda. PU was founded in 2004 by the Academic Medical Center - Center for Poverty-related Communicable Diseases (AMC-CPCD), the International Partnership for Microbicides (IPM) and several Rwandan partner institutions. Its objective is to mitigate the impact of the HIV epidemic, and to reduce the burden of other reproductive tract infections in Rwanda. PU comprises a research clinic (with facilities for gynecological examinations including colposcopy and HIV counselling and testing), a laboratory and an office.

Studies

Secondary analyses of data collected in the context of two studies conducted by PU from 2006 to 2009 are part of this thesis. The Kigali HIV incidence study (KHIS) was conducted on-site at PU (see below). The Reproductive Health Study (RHS; see below) was implemented by PU staff at the Women’s Health Clinic. This clinic was set up by the study team at the Kigali University Teaching Hospital with facilities for pelvic examination, colposcopy and cryoetherapy. Over the course of the study, gynaecologists were trained in colposcopy and cryoetherapy and after study completion the facilities were made accessible to all patients.

Kigali HIV incidence study (KHIS)

This study was conducted in preparation for a phase III microbicide trial. The primary objective was to estimate HIV incidence among women at high risk for HIV and other STIs, the target population of such a microbicide trial. HIV incidence data are important in the planning, design and the interpretation of HIV prevention methods and no such data were available from Rwanda. KHIS included a cross-sectional survey and a prospective observational study among high-risk women (HRW) at PU in Kigali, Rwanda. The collection of samples for HPV detection enabled us to look at the epidemiology of HPV among HRW in Kigali, as well.
Reproductive Health Study (RHS)

The RHS was a case-control study with the primary objective to study the aetiology, risk factors and determinants of infertility in Rwanda, with emphasis on the link with HIV/STIs. Among the fertile control couples samples were collected for the detection of HPV which allowed us to analyse concordance rates of HPV among heterosexual couples.

OUTLINE OF THE THESIS

Determinants of exposure to HPV are similar to those for most STIs. Determinants of susceptibility and infectivity are much less well established. In Chapter 2 these knowledge gaps are described using a literature review – including gaps in the understanding of interactions between HPV, HIV and other STIs, the role of mucosal immunology, human microbiota at mucosal surfaces, host genetic factors and hormonal levels on HPV susceptibility and infectivity, and the level of effectiveness of some primary and/or secondary preventive measures other than HPV vaccination for HIV.

Chapter 3 reports on baseline prevalence of HIV and other STIs, HIV incidence rates over time, participant accrual and retention rates, and incidence of pregnancy and STI among high-risk cohort participants in the KHIS study.

Chapter 4 focuses on the incidence, prevalence and persistence of type-specific HPV infection among the KHIS participants. Chapter 5 addresses the association between prior HPV infection and HIV acquisition among KHIS participants. Linkage to HIV care of newly diagnosed HIV positive high-risk women is discussed in Chapter 6. Quantitative results collected during KHIS are combined with qualitative results collected during focus group discussions with a selection of KHIS participants. The HIV/AIDS epidemic in sub-Saharan Africa is mainly heterosexual and vaginal penetrative intercourse is the main route of HIV transmission. However, the contribution of heterosexual anal intercourse to HIV transmission is not known. In Chapter 7 the prevalence of heterosexual anal intercourse among high-risk women in KHIS is addressed as well as its association with other risk behavior. Data from a twin-study conducted in Mombasa, Kenya were also included.

The transmission potential of HPV is currently not known, as was described in Chapter 2. A frequently used proxy of transmissibility is the concordance rate of HPV infection in couples. Chapter 8 discusses the type-specific concordance rates among fertile couples participating in RHS.

As the term ‘sexually transmitted infections’ unequivocally indicates – the different pathogens share their mode of transmission. Therefore one cannot try to prevent one STI without taking into account the ongoing epidemics of other STIs. Chapter 9 aims to give a brief overview of primary and secondary STI prevention programs and to put the results of the preceding chapters in such context.
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