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The effect of HAART on cervical intraepithelial neoplasia in women with HIV: a systematic review

Tsitsi Mildred Magure, MD
Department of Obstetrics and Gynaecology,
University of Zimbabwe

Abstract

Objectives: to review studies on the effect of antiretroviral therapy on the short term incidence, prevalence, regression, recurrence and the progression rates of pre-malignant conditions of the cervix in women infected with HIV.

Outcome measures: the effect of HAART therapy on the incidence, prevalence, regression, progression and recurrence rates of cervical intraepithelial neoclassic.

Inclusion criteria:

prospective or retrospective studies, either comparative or non-comparative, that present data on regression, progression, recurrence, incidence or prevalence rates of cytologically or histologically diagnosed cervical intraepithelial neoplasia

Exclusion criteria: Studies with incomplete data for analysis were excluded

Study population: HIV positive women receiving HAART. Comparative groups were:

- HIV positive women with cervical intraepithelial neoclassic who had not been commenced on antiretroviral therapy
- HIV positive women with cervical intraepithelial neoplasia on any other antiretroviral therapy other than the HAART combinations
- HIV negative women with cervical intraepithelial neoplasia

Materials and methods: a systematic review of studies with results on the effect of HAART on CIN was conducted. Electronic databases were searched; reference lists of identified studies were searched.

Results: Seven studies were included in this review with a total of 1018 HIV infected women. The studies were carried out in three developed countries (America, France and Italy). Two studies assessed the effect of HAART on the prevalence rates of CIN, while the other five evaluated the effect of HAART on the recurrence, progression and regression rates of CIN. One study found a statistically significant decrease in prevalence rates with HAART use. One study showed a non-statistically significant decrease in the prevalence rates with HAART use. Three studies showed increased rates of regression rates with HAART use, one study showed that regression rates were comparable in all the groups and while one showed statistically significant increase in progression rates with HAART use.

Conclusions: The question of the effect of HAART on CIN has not been adequately addressed by the studies in this review. The current recommendations of close cervical cancer screening surveillance in women infected with HIV should still be followed even in women on HAART until there is enough evidence to suggest otherwise.

There is still a need to conduct large multicentre trials to address this question.

Introduction

Cervical cancer remains a leading cause of mortality from cancer in developing countries. There are about 500 000 new cases of cervical cancer every year, 80% of them occur in developing countries (1). The natural history of cervical cancer is well known, with a well defined pre-malignant state called cervical intraepithelial neoplasia (CIN).These pre-malignant changes occur on the transformation zone of the cervix. Some of the risk factors for the development of these lesions include early onset of sexual intercourse, multiple sexual partners, partner with multiple sexual partners, sexually transmitted infections especially with genital human papilloma virus (HPV), cigarette smoking, low socio-economic status and immune suppression. It takes an average of about 10years for CIN to progress to invasive cervical cancer. About 60% of low-grade CIN regress spontaneously, and 32%of high-grade CIN (2-4).
Epidemiological studies have shown that infection with a subset of genital HPV is a major risk factor for the subsequent development of high-grade CIN and cervical cancer(5-6).This has been supported by results from the recombinant DNA technology and molecular gene cloning. Those results have shown that the E6 and E7 genes of this subset of HPV infections are oncogenes that deregulate key cell cycle control mechanisms and thereby predisposing the infected cells to neoplastic changes(7-8).The most common high risk HPV types are types16 and 18.The other high risk HPV types include types 31,33,35,39,45,52,56,and 58.

The role of infection with the Human Immunodeficiency Virus (HIV) and its link with HPV and cervical intraepithelial lesions has been a subject of research for some time. Cervical cancer is one of the AIDS defining malignancies. There is evidence that infection with HIV increases the risk of both the infection with the high risk HPV subtypes and the development of high-grade CIN (9-13). This risk increases with increasing immune suppression. This is thought to be due to that the immune suppression caused by HIV leads to proliferation and reactivation of dormant HPV infection, leading to an increased risk of cervical cancer. Antiretroviral therapy can restore the immunity in HIV-positive patients through the numerical restoration of the cd4 lymphocyte count. This restoration of immunity has been shown to be protective against other AIDS defining malignancies like lymphomas and Kaposi sarcoma (14-15).This protective effect has not been evaluated for genital HPV infection and the development of cervical intraepithelial lesions. The aim of this review was to look at studies that have assessed the effect of antiretroviral therapy on the incidence, prevalence and the natural course of cervical intraepithelial neoplasia in women infected with HIV.

Objectives

The objective was to review the literature on the effect of antiretroviral therapy on the short term incidence, prevalence, regression, recurrence and progression rates of pre-malignant conditions of the cervix in women infected with HIV.

Outcome measures

- The effect of HAART therapy on the incidence of cervical intraepithelial neoplasia
- The effect of HAART therapy on the regression, progression and recurrence rates of cervical intraepithelial neoplasia

Inclusion criteria

Studies that were included for this review met the following criteria:

1. prospective or retrospective studies
2. either comparative or non-comparative studies
3. have data on either regression, progression or recurrence rates of CIN
4. have data on either incidence or prevalence rates
5. cytological or histological diagnosed cervical intraepithelial neoplasia

Exclusion criteria

Studies with incomplete data for analysis were excluded.

Study population

Women of any age group who had been commenced on highly active triple antiretroviral therapy (HAART). HAART was defined as two or more nucleoside reverse transcriptase inhibitors, with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor.

The comparative groups were either

- HIV positive women with cervical intraepithelial neoplasia and who are not on antiretroviral therapy
- HIV positive women with cervical intraepithelial neoplasia on any other antiretroviral therapy other than the HAART
- HIV negative women with cervical intraepithelial neoplasia

Cervical intraepithelial neoplasia was classified using the Bethesda classification. The outcome measure was defined as a change from one group to another, which could either be regression or progression or persistence at the same level. The categorical effect on each class was not differentiated since the major aim was to determine the trend of movement of the disease.

Materials and methods

A systematic review of reports presenting results on the effect of triple antiretroviral therapy on cervical intraepithelial neoplasia was conducted. An electronic search was performed, searching the following databases: PUBMED,MEDLINE,ONCOLINK. A general web search through GOOGLE was performed. Manual search was performed at the Library of the World Health Organization, Geneva and the Geneva Medical School libraries.

For the electronic search, the following words were used:

- Cervical intraepithelial neoplasia
- Squamous intraepithelial lesions

- Antiretroviral therapy
- HAART

All full texts of the relevant studies were critically appraised regarding the study design, sampling, characteristics of the population studied, setting and type of data reported.

Results

Seven studies were included in this review with a total of 1018 HIV infected women. The studies were carried out in three developed countries (America, France and Italy).Of the seven studies included for the analysis, two assessed the effect of HAART on the prevalence rates of CIN, while the other five evaluated the effect of HAART on the recurrence, progression and regression rates of CIN.

Discussion

There is still limited data available on the effect of HAART on cervical intraepithelial neoplasia evolution in women infected with HIV. The few studies that have looked at the effect of HAART on CIN have conflicting results.

HAART is very effective in increasing immunity and reducing viral load. This has been shown to improve survival in AIDS patients through the reduction of the risk of opportunistic infections and other malignancies like lymphomas and Kaposi sarcoma (14-15). Similarly, it is HAART may play a role in altering the course of HPV associated CIN in women and thereby decreases the development and progression of CIN. The studies included in this review have not agreed on the role of HAART on CIN (13-18).

It should be noted, however, that most of the studies had very small sample sizes, with very different methodologies. The largest of the studies (Women Interagency HIV Study) found that after adjusting for HPV infection, cd4 counts and Pap smear status, women on HAART demonstrated a greater chance of regression versus progression of CIN.

Another limitation of the study is that the study designs used were not the best to answer the question. The best design would have been randomized control trials, however, those would be ethically not acceptable since the benefits of HAART are well established now. The other problem is that patients are rarely receiving HAART for the primary prevention of CIN. This means that cervical neoplasia is always viewed as a secondary outcome in many of these interventions.

Conclusions

The question of the effect of HAART on CIN has not been adequately addressed by the studies identified and included in this review. The current recommendations of close cervical cancer screening surveillance in women infected with HIV should still be followed even in women on HAART until there is enough evidence to suggest otherwise. There is still a need to conduct large multicentre trials to address this question. This should be possible in the near future with the widespread availability and affordability of HAART in developing countries where both HIV and cervical cancer are major health problems.

Table 1: Summary of results from studies that looked at the effect of HAART on CIN
Three of the studies showed an increased rate of regression with HAART use, one study showed that regression rates were comparable in all the groups and one showed

Journal	Study design Sample	Results	OR(CI) p-value
1.American journal of OBGYN: Mar2001:184(4):538-43	Retrospective Two arms Sample size: 54HIVpositive women 17 on HAART 37 not on HAART	Regression rates of HAART vs not on HAART 0 vs 9/37(24%) Recurrence rates of HAART vs not on HAART 3/17(18%)vs26/37(70%)	P<0.05 P<0.05
2.AIDS 2002,SEP6:16(13): 1799-802	Prospective Two arms Sample size: 168HIVpositive women 96 on HAART 72 not on HAART	HAART associated with a higher rate of regression than in no HAART	HR1.93(1.14-3.29) P<0.01
3.Clinical infectious diseases2004, Mar:38(5):737-42	Prospective Multiple arms Sample size:201HIV positive women 22 not on HAART 74 on HAART 49 on non-HAART combinations 56 on both HAART and non-HAART combinations	Regression rates were comparable among patients in each of the 3 antiretroviral therapy groups. Sub-analysis showed that the rate of low grade CIN regression rate was higher among those receiving HAART than among those receiving other antiretroviral regimens	P=0.1259
4.Journal of infectious diseases2001,Sep:184(5):547-51	Prospective Comparative Sample size:163HIV positive women 74 on HAART 62 on monotherapy 27 not on HAART	Increased progression rates in women on HAART	3.5(1.01-12.1) P<0.047
5.Journal of the National Cancer Institute2004,Jul21:96(14):1070-76	Prospective Sample size:312HIV positive women 221 on HAART 91 not on HAART	Incidence of regression in percent per year(person-years of follow up) increased from 0%before HAART to12.5%after HAART	CI=9.9-15.1 P=0.002

statistically significant increase in progression rates with HAART use.

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