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Cervical cancer in women with HIV

By Lesley Odendal

Key points

- Cervical cancer is one of the major causes of death and illness in women globally.
- Cervical cancer is caused by some strains of human papillomavirus (HPV), and develops at the neck of the womb. It is more likely to occur in women over 40.
- Women with HIV infection have a higher risk of developing cervical cancer. Women with lower CD4 counts are more likely to have cervical abnormalities. HPV causes cellular changes in the surface tissue of the cervix long before the development of cancer. These changes are described as pre-cancerous lesions, or cervical intraepithelial neoplasia (CIN).
- CIN lesions are graded according to severity. Many grade 1 lesions will clear up on their own without treatment, and so will quite a few grade 2 lesions. However some lesions will continue to grow and may eventually develop into cancer. This is why regular screening can save women's lives.
- CIN can only be identified by screening, either using a PAP smear or by applying acetic acid or iodine solution to the cervix. The latter method of visual diagnosis is less accurate, but much more practical to deliver in resource-limited settings.
- CIN grade 1 and 2 may be treated with cryotherapy (freezing the lesions with liquid nitrogen to destroy them) but more serious lesions need to be removed by surgery.
- Progression of cervical cancer is more likely in women with HIV infection.
- Antiretroviral therapy reduces the risk of progression to cervical cancer in women with cervical abnormalities only modestly.
- Two vaccines are now becoming available that can protect against HPV infection. The vaccines are targeted against the specific types of HPV that most commonly cause cervical cancer. The vaccines do not protect against the development of CIN or cervical cancer in women already infected with these types of HPV.
- A trial is now taking place in South Africa to test how well one of the vaccines works in women living with HIV, and several other studies are taking place in the United States.
- If cancer develops this must be treated by a combination of surgery, radiotherapy and chemotherapy, depending on the extent of cancer spread. Radiotherapy and chemotherapy are not available in many resource-limited settings for reasons of cost and limited health infrastructure.
- Palliative care is important for all women receiving treatment for cervical cancer, especially those with limited or no treatment options.
- Pain control, and access to analgesic drugs, is essential.
- A cancer diagnosis will also lead to great psychological suffering and women and their families require support and counselling.
- The involvement of a palliative care team in end-of-life care is also important, and quality of life, pain and symptom management should be given just as much emphasis as clinical staging when making decisions about treatment.

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Theo Smart contributed the section on palliative care considerations.

Cervical cancer is a major cause of death in women

Approximately 274,000 of the half a million women who develop cervical cancer annually will die from the disease.¹ 85% of these deaths will occur in women in the developing world.² Cervical cancer is the second most common cancer in women globally and accounts for 13% of all female cancers.³ Most cases of cervical cancer are diagnosed in women who are over forty years old.⁴

The cervix is the lower part of the uterus that connects the body of the uterus to the vagina or birth canal. Cervical cancer is mostly (99%) linked to genital infection with the human papillomaviruses (HPV),⁵ of which there are over 100 types. Thirteen are considered 'high risk' for causing cancer (oncogenic).⁶ 70% of the world's cervical cancer cases are caused by HPV types 16 and 18. Note that these are not the same types of HPV that cause genital warts (and which have low risk for cancer).

Given the limited treatment options available for advanced cervical cancer, public health experts recommend expanding prevention and screening programmes to detect pre-cancerous changes in cervical tissue. "Cervical screening is acknowledged as currently the most effective approach for cervical cancer control," states policy guidance issued by the World Health Organization in 2002.⁷

Most industrialised countries, and some lower-resourced countries, have responded by launching screening programmes. The most efficient of these programmes detect and treat pre-cancerous abnormalities and early stage cervical cancer, preventing up to 80% of potential cervical cancer cases.⁸

However, in many resource-constrained countries, there are no screening programmes, and women present late for care and treatment. A 2006 pilot study to assess the need for cervical screening among women with HIV in Zambia showed that among a cohort of 150 women, almost one in five had signs suggestive of cervical cancer and only 6% of women had a normal PAP smear. Almost 50% had high-grade cervical changes.⁹

At the same time, two vaccines, which are highly efficacious in preventing pre-cancerous cervical lesions from the two predominant oncogenic types of HPV, are being marketed in many countries with the primary target being young adolescent girls. But policies have yet to be developed regarding availability of these vaccines in many of the poorer settings with the least access to care and treatment for women with cervical cancer.

Although HPV can cause other types of cancers (in men and women) this clinical review will focus on the management of cervical cancer in HIV-infected women. HIV-infected individuals are at higher risk of HPV infection and persistence and are infected by a broader range of HPV types. Women living with HIV have been found to be eight times more likely to develop invasive cervical cancers than women who were not HIV infected,¹⁰ and cervical cancer is an AIDS-defining illness.

In addition, HIV-related immunodeficiency may also impair the effectiveness of vaccination and treatment, although responses may improve with antiretroviral therapy (ART).

International treatment recommendations depend upon the stage of disease (see section on *Treatment*). After properly staging the cancer, different modalities of treatment appropriate to the stage of disease are generally recommended. These include cone biopsy (removal of a cone-shaped tissue sample from the cervix for examination or to remove cancer or pre-cancerous tissue), radical hysterectomy (complete surgical removal of the uterus, cervix, upper vagina, and parametrium), radiation therapy, and combined modality therapy with radiation and chemotherapy.

As one can well imagine, even the most basic of these modalities, cone biopsy, can be difficult for women in some resource-limited settings to access, although some international NGOs are working to change this by providing training on the more simple surgical procedures.

Even with access to treatment, the prognosis for women with advanced invasive disease remains poor, especially in resource-constrained settings. In such cases, it is better to honestly inform the patient and her family of whatever limited options for care may exist, their potential risks and costs and their likely outcome. Palliative care is essential as soon as the earliest stages of cervical cancer are detected, as the illness can cause tremendous anxiety. Advanced cervical cancer can be a very painful condition, physically and psychologically, so it is essential to provide palliative care to reduce pain and suffering associated with the condition and its treatment for the woman and her family. This may include avoiding over-medicalised care and non-curative treatments that may simply extend the period of suffering, and, instead, emphasising the provision of end-of-life care.

Causes, course and risk factors for cervical cancer

High risk HPV is estimated to cause all cervical cancer cases.¹¹ HPV is sexually transmitted, but not only through penetrative sex, it can be transmitted through *skin-to-skin contact*, such as penile to vulvar contact and other sexual contact for which people typically do not use condoms. For this reason, condom use seems to be less completely protective against acquiring HPV.¹² Like other sexually transmitted infections (STIs), the risk for acquiring HPV is increased for individuals with a higher number of recent sexual partners, other STIs and a younger age at initiation of sexual activity.^{13,14} One of the factors contributing to transmission of HPV however, is that an individual's sexual partner usually shows no signs or symptoms of being infected.

Because of the greater ease of transmission, HPV is the most common sexually transmitted infection. Some studies from the United States have estimated that three-quarters of sexually active adults are infected with HPV at some point during their lifetime.¹⁵ Although the number of sexual partners increases the risk, it is important to note that even women who have only had one partner during their lifetime are at some risk if their partner may have had more than one sexual partner. In fact, in one study following women over a 7-year period, 34% of older, postmenopausal women (median age of 56), became HPV-positive – even though most of them were monogamous.¹⁶

Although approximately 90% of HPV infections are cleared within two years and result in no symptoms, the remaining 10% of HPV infections that persist can progress to cervical cancer.¹⁷ Most cervical cancers begin in the cells lining the cervix. Normal cells of the cervix usually first develop pre-cancerous changes which may progress to cancer, although in the majority of cases these changes do not result in progression to cancer.¹⁸ The pre-cancerous changes

are graded as cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesions (SIL), and dysplasia.

There are two main types of cervical cancers, namely *squamous cell carcinoma* and *adenocarcinoma*. About 80 to 90% of cervical cancers are squamous cell carcinomas and cover the surface of the exocervix and in most cases begin where the exocervix joins the endocervix.

Most of the remaining cervical cancers are adenocarcinomas, which are becoming more common in women born since 1980. Cervical adenocarcinoma develops from the mucus-producing gland cells of the endocervix.

Persistent infection by oncogenic HPV-types is a prerequisite for the development of cervical cancer. HPVs are non-enveloped, double-stranded deoxyribonucleic acid (DNA) viruses in the family of Papilloma-viridae. The dominant cancer-causing type of HPV is HPV-16 in all regions, while the distribution of other HPV types varies among geographical regions. Some HPV genotypes rarely cause cancer but may cause benign or low-grade changes in cervical cells that may be indistinguishable by cytology or histology from those caused by HPV types with greater oncogenic potential.

HPV infections do not cause the body to induce a strong immune response and while half of all HPV-infected women will develop detectable antibodies, they will not be protected from re-infection by the same HPV type. The median time from infection to seroconversion is approximately 8–12 months, although immunological response varies by individual and HPV type.

The time between initial HPV infection and development of cervical cancer averages 20 years and occurs in stages:

- Persistent HPV infection may lead to CIN of grade 1, which is likely to resolve without treatment in the majority of cases. (One study has shown that consistent condom use after diagnosis of CIN-1 is associated with regression of cervical lesions.)¹⁹
- In a minority of women infected with HPV who develop CIN grade 1, lesions will progress to moderate (2) grade or severe (3) grade or to a precancerous lesion involving cervical glandular cells, called adenocarcinoma in situ (AIS).
- If untreated, CIN2–3 has a high probability of progressing to squamous cell cancer, and AIS has a high probability of progressing to adenocarcinoma (cervical cancer).²⁰
- However, at least one natural history study has shown that in women diagnosed with CIN 2 lesions, 50% of lesions were observed to regress within two years without treatment.²¹

(Treatment of CIN-1–3 is discussed in *Treatment* below).

Some oncogenic HPV types denote a worse prognosis. One study of women diagnosed with cervical cancer showed that 27% of women who had HPV 18-related tumours died of cervical cancer specific causes, compared to 18% of women with HPV 16-related tumours.²² Women with HPV 18-related tumors were twice as likely to die compared to women with HPV 16-related tumors. The average cervical cancer patient who dies loses approximately 25 years of life.²³

As noted earlier, HIV may increase the risk of progression of cervical cancer. While immune deficiency increases the risk of cervical cancer disease progression, the occurrence of cervical cancer is not dependent on immune compromise, unlike other AIDS-defining neoplasms such as Kaposi's sarcoma and non-Hodgkin's lymphoma. This is because HIV appears to alter the natural history of HPV infection, causing a much more rapid progression to high grade and invasive lesions that are refractory to treatment, or which regress more slowly. Some researchers suggest this more aggressive course may actually be due to an HIV-related

change in the molecular pathway leading to cervical cancer, possible due to an interaction between viral proteins, with HIV proteins enhancing the effectiveness of HPV proteins, and perhaps contributing to cell cycle disruption.²⁴

Detection of HPV infection increases rapidly within the first years after HIV seroconversion, suggesting that mucosal immune dysfunction occurring at an early stage of HIV infection may influence HPV-related diseases. A study showed that among HIV seroconverters, HPV infection prevalence was 20.3% before seroconversion, 23.6% at seroconversion ($p = 0.4$), and 49.1% after seroconversion ($p = .01$). Seroconverters had significantly lower HPV infection prevalence than women with prevalent HIV infection before and at seroconversion (41.8% and 45.9%, respectively) but had similar HPV infection prevalence to women with prevalent HIV infection after seroconversion (49.4%). HIV seroconversion was associated with newly detected HPV infection (adjusted hazard ratio [AHR], 4.02; 95% CI, 2.26-7.13) and increased risk of low-grade cytological abnormalities (AHR, 2.53; 95% CI 1.16-5.51) compared with HIV-negative women.²⁵

Additional risk factors that enhance the development of cervical cancer from precancerous lesions are immune suppression; multiparity; early age at first child delivery; long-term use of hormonal contraceptives; cigarette smoking and infection with other STIs such as chlamydia trachomatis and herpes simplex virus type 2.²⁶ Notably while condom use may not have prevented infection in the first place, there are studies suggesting that it may reduce progression — possibly because it protects against exposure to other STIs.²⁷

A study of Rwandan women who were both HIV and HPV-infected showed that risk factors for stage 3 cervical cancer included having been pregnant more than seven times (vs 0-2) malarial infection in the previous six months (vs never), and ≥ 7 (vs 0-2) lifetime sexual partners.²⁸

Screening for cervical abnormalities

There are three methods used to screen for cervical abnormalities: cytology through conventional Pap smear, HPV DNA testing and visual inspection with acetic acid (VIA).

Cytology:

Pre-cancerous cells in the cervix can be detected by a Papanicolaou test, commonly known as a Pap smear. During a Pap smear, an extended-tip wooden spatula or brush is used to gather cells from the outer opening of the cervix and the endocervix in what is called the transformation zone. The entire transformation zone should be sampled as this is where almost all high-grade lesions develop in the cervix. The sample is then smeared onto a glass slide and immediately fixed with a solution to preserve the cells. The slide is sent to a cytology laboratory where it is stained and examined using a microscope to determine whether the cells are normal and to classify them appropriately, using the Bethesda classification.²⁹

The Pap test takes less than five minutes to perform, is not painful, and can be done in an outpatient examination room. It is advisable to postpone taking a Pap smear if the woman is menstruating actively, has a clinically evident acute inflammation, or is pregnant.

In the mid 1990s, Liquid-based Cytology (LBC) was introduced in order to increase effectiveness. Instead of smearing cervical cells on a slide, the provider transfers the specimen from a brush to a preservative solution and it is sent to the laboratory for the slide to be prepared. LBC takes less time to interpret, has fewer false

negatives (increases the specificity) and there are fewer unsatisfactory specimens. However, it is also more expensive and laboratory technicians need increased training.³⁰

HPV DNA testing:

A sample of cells is collected from the cervix or vagina using a swab or small brush, and placed in a small container with a preservative solution. The container is sent to the laboratory where it undergoes molecular testing through a PCR CAN test. Detection of high-risk HPV does not necessarily mean that precancer or cancer is present; it indicates simply that there is an HPV infection. The woman is then followed up more closely and regularly for the development of pre-cancerous cells.³¹

Visual methods:

Visual inspection can be performed through Visual Inspection using Acetic Acid (VIA) or Visual Inspection using Lugol's Iodine (VILI). Abnormalities are identified by inspection of the cervix without magnification, after application of dilute acetic acid or Lugol's iodine (in VILI). When acetic acid is applied to abnormal cervical tissue, it temporarily turns white (acetowhite) allowing healthcare workers to make an immediate assessment of a positive (abnormal) or negative (normal) result. If iodine is applied to the cervix, pre-cancerous and cancerous lesions appear well-defined, thick, and mustard or saffron-yellow in colour, while squamous epithelium stains brown or black, and columnar epithelium retains its normal pink colour. VIA and VILI are promising screening alternatives in low-income countries because they do not use laboratory services.

³² This method is often used as a primary screening tool and in cases where abnormalities have been identified, cytology is used for staging purposes.

Challenges in cervical cancer screening and diagnosis in resource-limited settings

Cytology is the most commonly used screening method in industrialised countries. In industrialised countries, it is recommended that sexually active women receive a Pap smear (cytological screening) annually or every one to five years from the age of 18 onwards. This has resulted in a large decline in the annual incidence and resultant mortality of cervical cancer, as pre-cancerous lesions are detected and treated before they progress to invasive cancers.

Laboratory constraints and poor quality control are one of the reasons offered for why resource-limited countries have failed to implement effective cervical cancer screening programmes (see below) — but the lack of screening programmes has resulted in a high number of cases and deaths.³³

However, screening programmes may not need to screen women as frequently as the yearly Pap smear that was first recommended — and the burden of screening might also be reduced by targeting it to the most high-risk individuals.

Due to the fact that cervical lesions develop slowly over many years, many national guidelines are moving towards recommending Pap smears every three to five years. If a low-grade lesion is detected through the Pap smear, women should be advised to return for follow-up Pap smears in the following 12 months. Women with high-grade precursor lesions are further evaluated via colposcopy, biopsy, and subsequent treatment of confirmed lesions.

Studies have shown that after two or more negative Pap smears, even screening once every 10 years yields a 64% reduction in the incidence of invasive cervical cancer, assuming the test is

performed properly. Further studies based on this model indicate that once-in-a-lifetime screening may yield around 25–30% reduction in the incidence of cervical cancer.^{34,35,36}

Health planners should base their decisions on the target age group and frequency of screening on local prevalence and incidence of cervical cancer and related factors such as HIV prevalence, and availability of resources and infrastructure. According to the WHO,³⁷ when deciding on the target age group and screening frequency in the face of limited resources, planners should take into account the following:

- HPV infection is very common in sexually active young women, but most infections are transient.
- Only a small percentage of all HPV infections will lead to invasive cancer.
- Cervical cancer usually develops slowly, taking 10 to 20 years from early precancer to invasive cancer.
- Cervical cancer is rare before the age of 30 years. Screening younger women will detect many lesions that will never develop into cancer, will lead to considerable overtreatment, and is not cost-effective.
- Screening every three years is nearly as effective as yearly screening. If resources are limited, screening every 5 to 10 years – or even just once between the ages of 35 and 45 years – will significantly reduce deaths from cervical cancer.

The WHO thus recommends the following:³⁸

- New programmes should start by screening women aged 30 years or over, and include younger women only when the higher-risk group (such as HIV-positive women) has been covered. Existing organised programmes should not include women less than 25 years of age in their target populations (due to the fact that cervical cancer takes years to develop).
- If a woman can be screened only once in her lifetime, the best age is between 35 and 45 years.
- For women over 50 years, a five-year screening interval is appropriate.
- In the age group 25–49 years, a three-year interval can be considered if resources are available.
- Screening is not necessary for women over 65 years, provided the last two previous smears were negative.

Although cytological screening is being carried out in some developing countries and regions, the testing is often of poor quality and performed inadequately and inefficiently among the population.

According to Rengaswamy Sankaranarayana of the International Agency for Research on Cancer, “Substantial costs are involved in providing the infrastructure, manpower, consumables, follow-up and surveillance for both organised and opportunistic screening programmes for cervical cancer. Owing to their limited health care resources, developing countries cannot afford the models of frequently repeated screening of women over a wide age range that are used in developed countries.”³⁹

Some of the reasons for the poor performance of cytology in many countries include poor sample collection, poor slide preparation and poor quality screening and review. Cytology relies on cells having been sampled from an area of high-grade CIN which may only cover a small proportion of the cervix: poor sample taking can mean that no abnormal cells are collected.⁴⁰

In addition, smears need to be read in a laboratory by trained cytotechnicians, under the supervision of a pathologist, who has final responsibility for the reported results, human resources that many low-income countries do not have.⁴¹

As a result, systematic screening has had a very limited impact on the incidence of cervical cancer, despite the large numbers of

cytological smears taken in some countries in resource-constrained settings.

A cluster-randomised, controlled trial conducted in rural India to evaluate the effectiveness of a single round of HPV DNA testing, cytologic testing, or visual inspection of the cervix with acetic acid (VIA) in reducing the incidence of cervical cancer, as compared with a control group that received standard of care cytology in a previously unscreened, high-risk population in India found that a single round of HPV DNA testing was associated with a significant decline (53%) in the rate of advanced cervical cancers (hazard ratio for the detection of advanced cancer in the HPV-testing group, 0.47; 95% CI, 0.32 - 0.69 and associated deaths (hazard ratio, 0.52; 95% CI, 0.33 - 0.83) as compared with the unscreened control group.

By contrast, there was no significant reduction in the rate of death in either the cytologic-testing group or the VIA group, as compared with the control group. The reduction in the incidence of advanced cancers and deaths associated with HPV testing probably reflects the higher sensitivity of HPV testing to detect lesions with a high potential for malignant transformation than that of cytologic testing or VIA.⁴²

Another study found that HPV DNA testing generally detects more than 90% of all CIN2, CIN3 or cancer cases, and is 25% (95% CI: 15–36%) relatively more sensitive than cytology at a cut-off of low-grade squamous intraepithelial lesions (LSIL) but is 6% (95% CI: 4–7%) relatively less specific.⁴³

A study to determine the diagnostic utility of VIA compared with cervical cytology showed that the sensitivity for VIA was only 20% with a specificity of 97% while the sensitivity for cytology was 80% with a specificity of 99%, showing that cervical cytology was more useful than visual inspection with acetic acid to detect dysplasias or cervical cancer opportunistically.⁴⁴

A large randomised comparison of screen-and-treat strategies in South Africa which included 944 HIV-positive women found that HPV DNA testing (plus treatment as indicated) significantly reduced the incidence of CIN grade 2 or higher during 36 months of follow-up by 80% in HIV-positive women. In comparison VIA plus treatment reduced the incidence of CIN grade 2 or higher by 49% in HIV-positive women. While HPV-DNA testing would prevent 11.9 cases per 100 HIV-positive women screened, VIA would prevent 7.4 cases per 100 women, the researchers calculated.⁴⁵

A previous South African randomised study which recruited 6555 women, of whom 12% were HIV-positive, also demonstrated a lower risk of CIN grade 2 or higher after 6 or 12 months in women who underwent HPV DNA testing plus treatment as indicated when compared to a VIA group. A sub-group analysis of efficacy in HIV-positive women was not reported for this trial.⁴⁶

However the practical difficulties of implementing either HPV-DNA testing or cervical cytology in resource-limited settings remains great, due to lack of laboratory infrastructure for cytology and pathology and lack of trained staff capable of carrying out the tests and interpreting them. These models of screening also carry the risk of loss to follow-up: even if a lesion is identified, it may be impossible to get a woman back for treatment, or by the time she returns to the clinic, the lesion may have progressed to the cancerous stage.

Therefore, despite the Indian results and despite its low sensitivity, VIA screening is likely to remain the most feasible option in many settings. Low sensitivity means that many pre-cancerous lesions will continue to be missed. This is obviously problematic given the paucity of treatment options for cancer in most

low-resource settings, and emphasises the need for regular VIA screening.

Due to the increased risk of developing cervical cancer for HIV-positive women, it is recommended that HIV-positive women in developed countries receive Pap smears annually, especially if they have low CD4 counts.⁴⁷

Frequencies for VIA screening have not been evaluated or proposed in women with HIV infection.

Case study of 'see and treat' cervical screening in Zambia

In a discussion of their implementation of a cervical cancer screening programme for women with HIV in Zambia, Groesbeck Parham and colleagues described some of the challenges involved in getting a local screening system up and running.

They rejected HPV DNA testing due to cost, the need for patient recall and the low specificity of the test. Cytology was rejected in part because Zambia had only one trained cytotechnologist at the time.

Instead they opted to use VIA in nurse-led clinics, with the back up of digital cervicography, in which digital images of the cervix could be transmitted to specialists off-site. Digital cervicography was used as back-up in order to address some of the major shortcomings of the VIA method, notably, the imprecision with which the shapes identified by VIA correspond to neoplasia. It also provided a means of quality control on diagnostic decisions.

The digital photograph could be used to magnify the image of the cervix on a lap-top screen, and to explain the findings to the patient. If a result was indeterminate it could be sent to the on-call specialist for advice on what to do.

In cases where an acetowhite lesion with well-defined borders was identified women received cryotherapy immediately and scheduled for return visits after 1, 6 and 12 months.

More complex cases such as large-volume lesions, or those suspected of being extensive or invasive, were referred to the University of Zambia Teaching Hospital for biopsy or LEEP.

The programme was integrated into public health clinics and was not confined to women with HIV, in order to avoid stigmatisation, even though this population is the primary target. Extensive community sensitisation began even before the eight-week nurse training was completed, initially targeting key community stakeholders to explain why cervical cancer screening was important.

Nurses and clinic staff were also given detailed training.

Next, peer educators were trained to promote the screening programme in their locality, both by speaking in medical facility waiting rooms and by talking to friends and neighbours. Drama and radio were also used to pass on the message.

The scheme screened 25,000 women in three years and is now being replicated in Cameroon, South Africa and Botswana. The investigators say that their combination of low tech (VIA), high tech (digital imaging) and high touch (peer education) has the potential to get round some of the major barriers to cervical cancer screening and treatment in resource-limited settings.⁴⁸

Epidemiology of cervical cancer in HIV-positive women

Many studies worldwide have shown a higher prevalence of cervical intraepithelial neoplasia (CIN) among HIV-positive women than among HIV-negative women. In the HER study, one of the larger studies of HIV-positive women, CIN was present in 19% of

HIV-positive women and only in 5% of the HIV-negative women.⁴⁹ Similar results were found from the Women's Interagency HIV Study Group (WIHS)⁵⁰ and from a large study of women in Abidjan, Ivory Coast.⁵¹

Incident CIN is also more common among HIV-positive women. In a study conducted in New York the incidence of CIN among HIV-positive women was 8.3 per 100 person-years, compared with 1.8 per 100 person-years among HIV-negative women.⁵² In the WIHS, at least one abnormal smear was found during follow-up for 73.0% of HIV-positive women and 42.3% of HIV-negative women, although the detection of new high-grade squamous intraepithelial lesions (HSILs) was low in both groups.⁵³ The main factors associated with the incidence of abnormal cytological findings were HIV positivity, HPV positivity, lower CD4 count, and higher HIV RNA level.

A more recent study conducted in South Africa also showed a high prevalence and incidence of pre-cancerous cervical lesions in HIV-positive women. The study showed that women with lower CD4 counts were more likely to have abnormal Pap smears. A total of 2325 women in the study had a cervical smear between 2003 and 2009. Only 4% were taking HIV treatment at baseline, but a further 15% initiated therapy during follow-up. The women were followed for a median of 24 months.

At the time of the initial screen, 38% of women had pre-cancerous lesions. Their median CD4 cell count was 254 cells/mm³, which was significantly lower than the median of 351 cells/mm³ observed in women with normal cervical cytology ($p < 0.0001$). Each 100 cell/mm³ increase in CD4 cell count reduced the risk of low-grade lesions by 13%, and high-grade lesions by 18%.⁵⁴

A study of HIV-positive women in Thailand found the prevalence of cervical squamous cell abnormalities from 821 initial Pap smear screenings was 15.4%. During a follow-up period of 3.5 years (7 pap smears), the prevalence rose to 37%. There were no associations of subsequent 'atypical squamous cell of undetermined significance or higher grades' (ASCUS+) with age, pregnancy, contraceptive method, antiretroviral treatment, assumed duration of infection, or the CD4 count nadir level. However, the multivariate correlation analysis showed that women with a CD4 count <350 cells/mm³ had a significant correlation with ASCUS+ ($p = 0.043$).⁵⁵

369 HIV-positive women receiving care at the Jos University Teaching Hospital in Nigeria were screened for abnormalities. Cervical dysplasia was present in 107 (29.0%) women. However, cervical cytology was abnormal in 252 (68.3%). Among those with abnormal cytology, 145 (57.5%) women had ASCUS, 56 (22.2%) had low-grade squamous intraepithelial lesion, and 51 (20.2%) had high-grade squamous intraepithelial lesion. Median CD4 count was lower in women with dysplasia compared with those without (142 vs 170 cells/mm³; $p = 0.04$), while median HIV RNA viral load was higher in women with dysplasia (101781 vs 77479 copies/ml; $p = 0.002$). Low CD4 count (<200 cells/mm³) and evidence of HPV infection were significantly associated with cervical dysplasia.⁵⁶

Screening programmes for HIV-infected women have yielded good results in resource-poor settings such as Zambia. Researchers estimate that a cervical cancer screening programme for HIV-positive Zambian women prevented one death from cervical cancer for every 32 women screened.⁵⁷

Among the 6572 HIV-positive women screened, 3523 (54%) had abnormal results. Those women were either offered immediate cryotherapy, if they met treatment criteria ($n = 2062$), or were referred for further evaluation ($n = 1461$).

Forty-nine percent of the women referred for further evaluation underwent histological confirmation, which led to the diagnosis of 235 pre-cancers (CIN 2 or 3); 79 early-stage cancers (stage 1A-1B); and 36 late-stage cancers (>stage 2A). Most of the early stage cancers (78%) were stage 1A (micro-invasive).⁵⁸ (Staging is described below in the *Treatment* section.)

However, despite the need for increased screening of HIV-positive women, studies show that screening of HIV-infected women is not occurring at sufficient scale. One study in South Africa showed that the proportion of women undergoing at least one Pap smear at HIV primary health clinics after HIV diagnosis was as low as 13.1%. In most (70.2%) of the women who did receive a cytological examination, high-grade cervical abnormalities were revealed.⁵⁹ Many women across South Africa do not have access to Pap smears.⁶⁰

Even in a relatively well-resourced country such as Italy, there is often inadequate access to Pap smears for women living with HIV. In one study, 1002 HIV-positive women attending public health facilities were interviewed regarding self-reported access to Pap smears. Nine percent reported no history of Pap smear, and 39% had no Pap smear in the year prior to the date of questionnaire. The lack of Pap smear in the last year was significantly associated with being younger than 35 years (OR = 1.4, compared to age ≥45 years), lower education level (OR = 1.3), first HIV-positive test in the last two years (OR = 1.4), and CD4 count <200 cells/mm³ (OR = 1.6). No difference in history of Pap smear emerged by mode of HIV acquisition or AIDS status. Three hundred five (34%) women reported a previous abnormal Pap smear, and of the 178 (58%) referred for treatment, 97% complied.⁶¹

The screening that is provided for women with HIV can be haphazard and inefficient. For instance, a situational analysis of provincial cervical cancer programmes. In Argentina using data from an ad-hoc questionnaire sent to the leaders of cervical cancer prevention programmes in the country's 24 provinces found that screening in Argentina is mainly opportunistic rather than systematic, characterised by an estimated low coverage of between 3 and 41 % across provinces, coexisting with over-screening of women with greater access to health services, and an absence of quality control procedures.⁶²

Further research and screening data for cervical cancer need to be conducted and collated at the global and regional level in order for country programmes to improve coverage where needs are identified.

Prevention of cervical cancer through vaccination

There are currently two vaccines for HPV that are being marketed internationally as preventive vaccines, and are also endorsed by the World Health Organization (WHO). *Gardasil* provides protection from HPV types 6, 11, 16 and 18 and is manufactured by Merck. However, the vaccine has also shown a modest impact on other HPV strains such as types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, indicating that *Gardasil* may be able to prevent more cases of cervical cancer, and offer wider protection than originally estimated.⁶³

Cervarix provides protection from only HPV types 16 and 18 and is manufactured by GlaxoSmithKline (GSK). Both vaccines use recombinant technology, and are prepared from purified L1 structural proteins that self-assemble to form HPV type-specific empty shells or virus-like particles (VLPs). Neither vaccine contains live biological products or viral DNA, so they are non-infectious. The

mechanisms by which these vaccines induce protection have not been fully defined, but involve the development of cellular immunity.⁶⁴

In June 2007, the WHO Global Advisory Committee on Vaccine Safety judged both vaccines to have good safety profiles and identified no major safety concerns as both vaccines appear generally safe and well-tolerated based on available data from trials and post-marketing surveillance.⁶⁵

Both vaccines are intended to be administered to females before the onset of sexual activity before they have potentially been exposed to HPV. In most countries, recommendations state that girls should be vaccinated between the ages of 10 and 14 years.

Gardasil is given at baseline and is repeated at two months and six months. According to the manufacturer, if flexibility in the timing of the dose is necessary, a minimum interval of four weeks between the first and second dose, and a minimum interval of 12 weeks between the second and third dose are required.⁶⁶ *Cervarix* is given at baseline and again at one month and six month. Alternative schedules are being explored for both vaccines.⁶⁷

The overall combined estimate of HPV 16 and HPV 18 prevalence among cervical cancer cases in sub-Saharan Africa is 69.2%, which is consistent with the worldwide estimate of 70%.⁶⁸ In addition, the five most frequent HPV types among women with cervical cancer in sub-Saharan Africa according to ranking order are HPV 16, 18, 45, 33 and 35, a distribution which does not differ significantly from the worldwide distribution (HPV 16, 18, 33, 45 and 31).⁶⁹

However, about 50% of HIV-positive women with HPV 16 and/or 18 ICC cases are co-infected with another HPV type, so it is unclear whether the other HR types would be responsible for invasive disease in the absence of HPV 16 or 18.⁷⁰ One review has argued that these data suggest that current HPV vaccines containing HPV16/18 may potentially prevent fewer cases of cervical cancer among HIV-positive women.⁷¹

Neither vaccine can clear existing HPV infection or treat HPV-related disease.⁷²

The use of either vaccine is thus discouraged in women with existing HPV 16 or 18 infection as trials have shown that clearance rates of cervical cancer are not significantly different for women who received the full dose of the vaccine compared to those who did not in women already infected by these strains of HPV.

However, women who are already infected with some of the four strains of HPV that *Gardasil* protects against, are protected by the vaccine against pre-cancerous or cancerous cervical cell changes caused by the remaining cancer-causing strains.

A study showed that amongst women infected with between one or three strains of HPV that the vaccine protects against, *Gardasil* was 100% effective at preventing pre-cancerous or cancerous cervical cell changes caused by the remaining strain(s) with which the women were uninfected, at the time of vaccination. Over three years, the efficacy of the vaccine at preventing pre-cancerous or cancerous cervical cell changes due to the remaining strains was 91%. In addition, the vaccine had a 94% efficacy at preventing anogenital and vaginal lesions caused by the strain(s) of HPV with which the women were uninfected.⁷³ This suggests that vaccinating older, sexually experienced girls and young women could be of some value to women who are not infected by all four of the strains that *Gardasil* provides protection against.

The duration of protection is not yet known, but there is evidence of protection for at least six years after vaccination for both vaccines. Studies of both vaccines are currently evaluating longer-term efficacy.⁷⁴

According to the WHO, in settings where both HPV vaccines are marketed, the choice of which vaccine to use should be based on an assessment of the prevalence of the predominant type of HPV causing the highest prevalence of cervical cancer in the region; the target age group (girls aged between 9 and 13 years, or older females, and/or males) and which schedule of delivery is most convenient for the relevant population.⁷⁵

Mathematical models predict that vaccination programmes for young adolescent females will substantially reduce the incidence of cervical cancers associated with vaccine-related HPV types if coverage is above 70% and if protection lasts for more than ten years.⁷⁶

In the clinical trials of both vaccines, vaccinated persons were not significantly more likely to have serious or systematic adverse events than placebo recipients, but vaccinated persons were more likely to have mild, transient soreness, redness or swelling at the injection site than placebo recipients. Reports of fainting immediately after HPV vaccination have been noted in some countries, and hence, it has been recommended that all vaccinated person are observed for 15 minutes after vaccination.⁷⁷

HPV vaccines should not be given to people who have experienced severe allergic reaction after a previous vaccine dose or to a component of the vaccine; to pregnant women or people who have severe acute illness. *Gardasil* may be given to lactating women, while safety data for lactating women are not available for *Cervarix*.

To date, information on the immune response to HPV vaccination in HIV-infected individuals is limited to a study of 120 children aged 7–11 years in the United States, some of whom used antiretroviral therapy.⁷⁸ Currently, the safety and efficacy of HPV vaccines are now being evaluated in parts of Africa and in populations with high HIV prevalence (such as Khayelitsha in South Africa) but results are not yet available.⁷⁹

Other forms of HPV and cervical cancer prevention, which offer partial protection include reducing the number of one's sexual partners and postponing sexual debut.

Consistent condom use for the entire duration of sexual activity (not simply intercourse) may offer partial but not complete protection since HPV may be transmitted to and from genital tissue not covered by condoms.

Finally, a recent report suggests that circumcising men modestly reduces the risk of transmitting types of human papillomavirus associated with cervical and anal cancer to women. The studies in Uganda [showed](#) that circumcision reduced the risk of men acquiring high-risk forms of HPV associated with the development of cervical cancer in women by around 35%.⁸⁰

Treatment of pre-cancerous cervical abnormalities

Treatment of the pre-cancerous lesions identified by testing will vary somewhat according to the stage.

CIN-1:

Although some physicians may adopt a policy of watchful waiting in cases of CIN-1, given the high probability that lesions will regress without treatment, this is a higher-risk treatment strategy in settings where access to services is difficult or where there is a risk of loss to follow-up. If the lesion isn't dealt with at this stage, the more complex surgery needed for a more advanced lesion may come too late, or may be difficult to obtain. In settings where VIA is used as the main screening method and 'See and Treat' is the organising

principle for cervical cancer prevention, any obvious lesion will be treated, most likely with cryotherapy.

Cryotherapy involves the use of liquid nitrogen, which is blasted from a compressed cylinder of nitrous oxide gas, to freeze the lesion. The normal procedure is to freeze the lesion for three minutes, allow it to thaw for five minutes and then repeat the procedure. Common side-effects include bleeding, vaginal discharge and abdominal pain, but serious complications are rare. In their study of 'screen and treat' modalities among HIV-positive women in South Africa Louise Kuhn and colleagues observed that although women were advised to abstain from sexual intercourse for a month after the procedure, half still reported having sex during this period and less than 60% reported consistent condom use during this period.⁸¹

CIN-2:

Many lesions of CIN-2 grade may also be treated with cryotherapy simply because they are not recognised as such when VIA is the sole diagnostic procedure, but surgery is normally recommended in order to remove lower levels of the cervical epithelium. The most common surgical method in resource-constrained settings is loop electrosurgical excision procedure (LEEP), which uses a wire loop to cut the tissue of the cervix and then cauterise and seal the surface with an electric current. Alternatively, conisation may be necessary. This is a surgical procedure in which a cone of tissue is cut out of the cervix in order to remove any pre-cancerous cells that might have developed below the epithelial surface.

CIN-3:

The same treatment approach will apply for CIN-3. However in the most severe and/or recurrent cases hysterectomy may be proposed, especially in post-menopausal women. Hysterectomy requires access to surgery and anaesthesia, and may not be an acceptable option for women still in their child-bearing years.

Treatment of cervical cancer

Cervical cancer, like most other cancers, develops in stages. Depending on the stage of the development of the cervical cancer, different strategies of treatment will be necessary. The sooner the cancer is detected, the easier it will be to treat. The three main methods of treating cervical cancer are surgery, radiation therapy and chemotherapy. While the approach to the treatment of cervical cancer is generally the same for HIV-positive and HIV-negative women, new studies are showing that there may be differences in how immune-compromised individuals respond to treatment.

However, it is important to make the patient and her family partners in making these treatment decisions. There may be other factors specific to the patient and her family's cultural background, and socio-economic circumstances that affect whether a certain treatment modality is appropriate (see section on Palliative Care).

The following stages and types of treatment are used to grade the extent of the cervical cancer and decide upon the necessary treatment:⁸²

Stage 0:

This is called carcinoma in situ and corresponds to CIN-3. It is diagnosed when abnormal cells are found in the innermost lining of the cervix. These may spread to nearby normal tissue. See above for treatment approaches.

Stage 1:

This is when the cancer has formed and is found in the tissues only of the cervix. In stage 1A, the cancer is no deeper than 5mm and no more than 7 mm wide and can only be seen with a microscope. In Stage 1B, the cancerous tumour can be seen without the use of a microscope and is more than 5mm deep and 7mm wide.

The treatment for stages 1 and 2 can include a combination of internal and external radiation therapy, a radical hysterectomy and removal of lymph nodes and chemotherapy.

Stage 2:

In stage 2A the cancer has spread beyond the cervix to the upper two thirds of the vagina but not to tissues around the uterus, while the cancer has also spread to the tissues round the uterus in stage 2B.

Stage 3: In stage 3A, the cancer has spread to the lower third of the vagina, but not to the pelvic wall. In stage 3B, the cancer has spread to the pelvic wall and in some cases the tumour may be so large that it blocks the ureters, which are tubes which connect the kidneys to the bladder. This can cause the kidneys to enlarge or stop working all together. The cancer cells may at this stage also spread to the lymph nodes in the pelvis.

For stages 3 and 4, the remaining treatment options are internal and external radiation therapy, combined with chemotherapy.

Stage 4: During stage 4A, the cancer will have spread to the bladder or rectal wall and may also have spread to lymph nodes in the pelvis. In stage 4B, the cancer will have spread beyond the pelvis and pelvic lymph nodes to other places in the body, such as the abdomen, liver, intestinal tract, or lungs.

Treatment approaches involving radiation and chemotherapy are not widely available in sub-Saharan Africa or Asia. A 2008 review on cancer treatment in sub-Saharan Africa noted that radiotherapy was available in only 23 of 53 countries, and that although the number of units able to offer radiotherapy had increased by 30% in the previous decade, this expansion was taking place predominantly in countries already able to offer radiotherapy.⁸³

One of the few case series reports on radiotherapy outcomes in cervical cancer cases in sub-Saharan Africa noted that late presentation was also a major barrier to effective use of radiotherapy. Only one-third of presenting patients were suitable for radiotherapy due to extensive spread of cancer, and one in five had been symptomatic for at least a year before reaching the hospital. The median duration of symptomatic disease was eight months.⁸⁴

Chemotherapy also remains out of reach in many settings. Cisplatin-based chemotherapy in combination with radiation has become the standard of care for patients with locally advanced cervical cancer in industrialised countries, but access is limited by cost in resource-constrained settings. Cost effectiveness data are still lacking for resource-limited settings. However many women in sub-Saharan Africa would be unlikely to qualify for cisplatin-based chemotherapy due to contraindications, most notably anaemia and hydronephrosis (swelling of the kidney due to obstruction of urinary flow, as a consequence of the growth of the cancer).⁸⁵ In more advanced invasive disease, combination chemotherapy could include cisplatin and topotecan or cisplatin and paclitaxel.^{86,87}

According to Nomfundo Eland, manager of the National Women's Right Campaign run by the Treatment Action Campaign (TAC) in South Africa, cervical cancer treatments are not always immediately available in countries like South Africa, but even more so in poorer countries of the world. "There is often a waiting list. We have statements by women who told us that they could only get treatment six months after their Pap smears came out positive. This

increases their chances of their cervical cancer developing to more serious stages," explained Eland.⁸⁸

Responses to treatments for CIN and cervical cancer in HIV-positive women

The main risk factors associated with recurrence of cervical cancer in HIV-positive women following treatment were the severity of immunosuppression according to CD4 count and the presence of residual diseases. However, cervical intraepithelial neoplasia (CIN) has also been found to recur in cases when no residual disease was present following treatment.

Recurrence rates are higher in HIV-positive women than in HIV-negative women. For example, one study showed that a second excisional procedure permanently removed the disease in HIV-negative women, but in HIV-positive women CIN was found to recur and progress despite multiple treatments.⁸⁹

A recent study has also shown that HIV-infected women with lower CD4 counts were more likely to experience progression of cervical cancer. Patients with a CD4 cell count below 200 cells/mm³ were almost twice as likely as those with a CD4 cell count above 500 cells/mm³ to experience disease progression ($p < 0.0001$). Taking ARVs reduced the risk of disease progression by 28% ($p < 0.05$).⁹⁰

However, CD4 cell counts may not be the best measure to determine whether an HIV-positive woman's immune system is able to tackle human papillomavirus (HPV) infection. One study suggests that skin prick testing is a better measure than CD4 counts.⁹¹ Cutaneous anergy testing – or skin prick testing – evaluates the ability of the body to mount a specific type of immune response and reflects the number and the capacity of certain immune cells throughout the body, not just in the skin. A study showed that women who had anergy – no reaction to the skin prick test – were 70% more likely to have cervical neoplasia (odds ratio 1.70, 95 CI 1.16 to 2.48) and 24% more likely to be infected with a strain of HPV (odds ratio 1.24, 95 CI 0.99 to 1.56). These figures were irrespective of CD4 count or presence of HIV.⁹²

Information about the impact of HIV therapy on the clearance of cervical human papillomavirus is inconsistent. Some studies suggest that the immune restoration that results from antiretroviral therapy helps clear the infection, but other research has found no evidence of this. Starting antiretroviral treatment does not reduce the incidence or prevalence of cervical infection with HPV according to a recent study, where researchers found that all types of the virus persisted, despite ARV initiation, including those associated with a high risk of cervical cancer. The study also found no evidence that better increases in CD4 cell count after starting HIV treatment increased the chances of clearing cervical infection. In addition, many patients who were taking ARVs acquired HPV infection.⁹³ The study found that incidence of HPV 16 was 6.54 per 100 person years before HIV treatment was started and 6.67 per 100 person years after. Similarly, the incidence of HPV 18 was 4.66 per 100 person years in the period before antiretroviral therapy was started and increased to 6.26 per 100 person years after patients started taking anti-HIV drugs.

Women with lower CD4 counts are also more likely to experience CIN treatment failure. A study showed that in the women with a CD4 count of below 200 cells/mm³, CIN treatment failure occurred in 71% (27 of 38). For those with a CD4 count between 201 and 500 cells/mm³, CIN treatment failure occurred in 57% (32 of 56) and in 20% (4 of 20) for HIV-infected women with a CD4 count greater than 500 cells/mm³. Women with a CD4 below 200 cells/mm³ were

2.93 times more likely (95 CI 1.06-8.11) to experience CIN treatment failure than those with a CD4 count above 500 cells/mm³.⁹⁴

The same retrospective cohort study of 136 HIV-infected women who had a loop electrosurgical excision procedure (LEEP) or cone procedure for CIN suggest that cervical conization may be superior to LEEP in the treatment of CIN in HIV-infected women. Women who were treated using LEEP were 76% more likely to experience CIN treatment failure (RR = 1.76; 95% CI: 1.17 – 2.64).⁹⁵

Cryotherapy has been shown to be an effective treatment to prevent the reactivation of HPV infections among HIV-positive women. The impact of cryotherapy on newly detected HPV infections was examined among 540 HIV-infected women, aged 35 to 65 years. Women in the cryotherapy group were 55% less likely to have newly detected HPV than women who did not receive cryotherapy (95% CI 0.28 to 0.71).⁹⁶

Palliative care considerations for cervical cancer in resource-limited settings

Cervical cancer is a diagnosis that can have profound implications for a woman's physical, social, emotional wellbeing and quality of life – and quite frequently affects her relationship with her partner and family. In many cases, such as when she presents late for care with advanced disease, it is a diagnosis of terminal disease, particularly in resource-limited settings, where staging (which can require sending out specimens for cervical cancer cytology and histology studies that are only available at regional or central laboratories) and treatment options are more limited.

According to a 2004 report from the Diana, Princess of Wales Memorial Fund, "It is estimated that 80% of cancer patients have advanced incurable disease at first presentation," which together with the "inadequate diagnostic facilities, poor availability of chemotherapy and radiotherapy, and absence of the WHO step ladder approach [to pain management], all increase the need for improved adequacy of cancer pain control in Africa."⁹⁷

Healthcare workers in HIV programmes need to be aware that in many cases of cervical cancer, the goal of treatment may need to be purely palliative, rather than curative – and treatment should be directed at alleviating the pain and suffering caused by the condition rather than at extending life.

Any diagnosis of advanced cervical cancer in a woman living with HIV who is already in routine care represents a failure and missed opportunity on the part of the HIV programme and health system. Given the high burden of cervical cancer in African women living with HIV, and the difficulty treating it once it progresses to more advanced stages, the case for routine screening to increase early detection is obvious – though the case may need to be made more forcefully to the bi- and multilateral funders of HIV programmes to help pay for this essential aspect of women's health care.

But any HIV programme that does perform Pap smears or HPV screening in their clients needs to be prepared for the results. Nurses or counsellors presenting this news to a woman need to understand what cervical cancer is and how it may potentially affect the woman's life, and how to educate the woman, and crucially, her partner about it.

Even before significant symptoms have developed, a cervical cancer diagnosis can cause great psychological suffering due to self-blame, mistaken beliefs about the origin of the cancer (such as when she contracted HPV), and she may experience changes in self-image, self esteem fears about what having cancer means, and worries about how it will impact upon her children and family.^{98,99}

Women with cervical cancer may become unable to have sex, or lose interest or pleasure in it, and the potential impact that the diagnosis, the advancing disease, treatment and its complications can have on women's male partners should not be underestimated. In many societies, it is not uncommon for husbands to leave their wives if they have gynaecological illnesses, if they become unable to bear more children or if they are unable or unwilling to have sex.

For instance, one palliative care organisation, the U Hla Tun Hospice (Cancer) Foundation in Myanmar was launched by a bereaved father because of this problem.¹⁰⁰ After his daughter died of cancer, he launched the organisation to help other cancer patients especially women with cervical cancer who were abandoned by their husbands. These women would otherwise have little or no support, so in addition to providing hospice care, the foundation has created a fund so that these patients can receive the necessary funeral rites when they die.

HIV programmes should integrate a palliative care approach, which aims at careful consideration and management of their patient's physical and psychosocial suffering, looking at their patients needs holistically, into the provision of HIV care as it could lead to improved outcomes, better client satisfaction, and reduced losses to follow-up.

However, in the case of cervical cancer, it may be particularly useful for health services and HIV programmes to develop a working partnership with a local palliative care team or programme, which can assist the programme from diagnosis and initial counselling throughout the course of managing the illness.

Palliative care organisations in Africa have developed great expertise working with cancer patients. Palliative care teams can help in the assessment of pain and quality of life in women with cervical cancer, help connect women to supportive care, provide advice on treatment options and approaches that may ameliorate some of the symptoms of cervical cancer that cause the woman the most distress, and help organise hospice and end-of-life care when the need arises.

Symptom, pain and quality of life assessments that are appropriate for the local population (and in the client's language – local palliative care organisations should have expertise in this area) may be just as important as staging in directing the course of treatment and care. Invasive cancer can lead to a number of complications including severe gynaecological pain, urinary retention, or conversely vesicovaginal fistula that lead to urinary incontinence, and unpleasant vaginal discharges that can lead to stigma and cause the woman great distress.¹⁰¹

A wide range of treatment-related factors can reduce the quality of life of women as well. According to a recent report from Brazil, these include "functional damage secondary to treatments such as pelvic surgery involving the removal of parts of the female genital anatomy and radiation, which damages the vaginal mucosa and epithelium; [and] side effects of chemotherapy, which in part are similar to those radiotherapy can cause, such as nausea, vomiting, diarrhoea, constipation, mucositis, weight changes and hormonal changes."¹⁰²

Treatment of early stage disease of pre-cancerous lesions and high-grade CIN lesions has a high rate of success whether using excisional and ablative techniques (which generally must be guided by cytology and colposcopy) or cryotherapy of all women who screen positive (which is increasingly the approach in low-resource settings with less access to cytology).¹⁰³

Physical pain should be managed in accordance with the WHO step ladder approach to pain management, which will require access to sufficient supplies of opioid drugs.

Radiation and chemotherapy for cancer remains very expensive, not widely accessible and is often restricted to curable cases of cervical cancer. Antiemetic drugs should be given to relieve the side-effects of chemotherapy in those who can receive treatment. In more advanced stages of cervical cancer, curative treatment may not be possible. Nevertheless, where it is available, low dose (single-fraction) radiation therapy may be useful in reducing tumours that causing discomfort or obstructions. It is often used on an individualised basis to control bleeding, pelvic pain, or urinary or partial large bowel obstructions from pelvic disease.

The Palliative Care Toolkit, makes the following recommendation for managing vaginal discharges, which are a common symptom of cervical cancer.¹⁰⁴ Because it is usually smelly, it causes the woman embarrassment, distress and stigma, but the following recommendations may help manage it:

Treat

- Sexually transmitted disease (follow local guidelines)
- Vulvo-vaginal candida (thrush) with antifungal pessaries, e.g. clotrimazole, miconazole or single oral dose of fluconazole 150mg

Care

- Sit in basin of water with a pinch of salt twice daily.
- Use cotton pads made from old clothes.
- Plastic pants with elastic can be made locally.
- Make sure soiled pads and linen are washed and changed regularly.
- Discourage putting foreign bodies in the vagina.

Prescribe

- Metronidazole tablet (200mg) can be inserted daily as a pessary into the vagina or crushed and the powder applied.

According to one case report, several other palliative measures may prove useful.¹⁰⁵ For instance, urinary retention should be treated either by intermittent catheterisation or by the insertion of a Foley catheter, that should be changed every fortnight. In cases where the cancer is advancing aggressively, urinary diversion procedures may not be justified in cases of vesicovaginal fistula, but adult diapers may help keep the patients more comfortable.

While antiretroviral therapy may improve prognosis and response to treatment early in the course of cervical cancer, some palliative care experts question whether it, or any other treatment that may extend life but not lead to curing the disease, is warranted, or advisable in a patient with advanced cervical cancer. Pure palliative therapy and end of life care should rather be emphasized.

As JV Larsen, in a report in the South African Medical Journal on managing cervical cancer in a district hospital (Eshowe Hospital in KwaZulu Natal) wrote, "Lastly, it must be kept in mind that people are much more than bodies. Other team members should be recruited as required. Clergy should be part of the team, offering spiritual consolation to help cope with the fear of death. The social worker should be part of the team, to help with difficulties with grants, travel costs and the care of young children. The family should be assisted in every way to complete the work necessary in their relationships. When these processes are facilitated by sensitive medical staff, approaching death can become an occasion for rapid personal growth for the patient and her family."

Conclusion

For HIV-infected women in particular, there are many research questions that need to be examined in order to better diagnose,

prevent and treat cervical cancer. The uptake of screening for HIV-infected women has been shown to be low. No evidence regarding the safety of HPV vaccines for HIV-infected women exists, although trials are currently underway. Some studies have suggested that HIV-infected women respond differently to the treatment of cervical cancer compared to HIV-negative women. However, research on this matter is far from complete and the current findings suggest that there may be other factors relating to the treatment of cervical cancer in HIV-infected women that are unknown.

Until recently, there were no data on HPV vaccination among those infected with HIV. Clinical trials are underway in HIV-positive women in South Africa and results are eagerly awaited from this study. In addition, initial results from a quadrivalent vaccine trial of 126 perinatally infected HIV-infected children (7–12 years) in North America have shown that the vaccine is generally safe and nearly 100% seroconverted although antibody titres for HPV 16 and 18 were lower than in HIV-negative children.¹⁰⁶

Given that HIV-positive women are more likely to develop cervical cancer and that the prevalence of cervical cancer is higher in resource-poor settings where the HIV prevalence is also usually higher, researchers must endeavour to gather data to ensure the prompt diagnosis and treatment of this killer disease.

Resources

The African Palliative Care Association and the Hospice Palliative Care Association of SA offer a Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa (<http://www.apca.co.ug/publications/clinicalguide.htm>)

Help the Hospices has helped to create a Toolkit that is designed to equip, empower and encourage health workers in resource-limited settings to integrate palliative care into their work and their communities: The Palliative Care Toolkit

(<http://www.helpthehospices.org.uk/EasySiteWeb/GatewayLink.aspx?alld=6147>)

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WHO-UNITAID call for interest

Call for Interest from individuals wishing to apply for membership of the Advisory Group on Funding Priorities ("AGFP")

UNITAID's mission is to contribute to scaling up access to treatment for HIV/AIDS, malaria and tuberculosis (TB) for people in developing countries by leveraging price reductions of quality drugs and diagnostics, which currently are unaffordable for most developing countries, and to accelerate the pace at which they are made available.

The Advisory Group on Funding Priorities ("AGFP") is an independent expert panel that assists in identifying, consistent with the UNITAID Strategy endorsed by the Board, potential priority niches of high-market and public health impact to be funded by UNITAID. Members of the AGFP are high level experts with academic or major organizational experience in their fields of work, which will also be the areas of UNITAID's focus. The panel is broadly constituted, comprising Members with expertise in the public health aspects of UNITAID's areas of work, health economics, market dynamics, programme management, health research and new product development.

For more details on how to apply please visit the UNITAID website:

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Submissions should be sent to: saara.reid@hlsp.org to arrive no later than Sunday 20th March 2011.

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A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

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