

# GESIDA/National on AIDS. Recommendations for the diagnosis and treatment of Kaposi sarcoma and cancer of the cervix in patients infected by the human immunodeficiency virus

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## Introduction

Malignant tumors are one of the most significant complications of the human immunodeficiency virus (HIV). Some, such as Kaposi sarcoma (KS), primary central nervous system lymphoma, systemic non-Hodgkin's lymphoma and cancer of the cervix have been considered as AIDS-defining diseases since the beginning of the pandemic. The introduction of highly active antiretroviral therapy (HAART) in 1996 radically changed the natural history of HIV infection and drastically reduced the incidence of tumors such as primary central nervous system lymphoma and KS, although its impact on other types of cancer has been smaller.

The GESIDA (Grupo de Estudio del Sida) and PETHEMA (Programa de Estudio y Tratamiento de las Hemopatías Malignas) recommendations on the diagnosis and treatment of HIV-associated lymphomas have been brought together in a recently published document<sup>1</sup>. This document aims to offer some recommendations on the diagnosis and treatment of AIDS-associated KS and cervical cancer.

## Diagnosis

KS usually presents as raised or flat violet-red cutaneous lesions, that are generally asymptomatic and usually measure between 0.5 and 2 cm. They can affect any area of the skin, oral mucosa or gastrointestinal tract, and can occasionally cause bleeding or perforation. Less frequent, although more severe, is pleuropulmonary involvement in the form of bilateral interstitial infiltrates, focal alveolar patterns, peribronchial and perihilar infiltrates, and pleural effusion.

Early diagnosis is based on careful examination of the skin and oral cavity at each clinical visit. Diagnosis of cutaneous KS is clinical and confirmed histologically by biopsy.

Diagnosis of pulmonary or gastrointestinal KS is made by endoscopy, which enables us to see the typical violet lesions. Biopsy is not usually useful for diagnosis due to the submucosal location of the lesions.

## Systemic treatment of AIDS-associated Kaposi sarcoma

When considering treatment of KS, it must be taken into account that standard oncological criteria are not suitable for evaluating therapeutic response to this tumor. For example,

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it is possible to achieve complete remission (confirmed by biopsy) of nodular lesions that do not disappear or to reduce their diameter, although they persist as pigmented residual macules<sup>1</sup>. The oncology committee of the Aids Clinical Trials Group (ACTG) published recommendations in 1989 for staging and evaluating KS<sup>2</sup>. A subsequent study was performed to validate the classifications, and it was observed that prognosis depended not so much on the degree of systemic tumor involvement as on the CD4 lymphocyte count. Thus, median survival was not reached in patients with a CD4 count  $\geq 150/\mu\text{l}$  and little tumor involvement, was 35 months for those who had CD4  $\geq 150/\mu\text{l}$  and extensive tumor involvement and only 12 months for those with CD4 counts  $< 150/\mu\text{l}$  regardless of tumor involvement<sup>3</sup>.

Systemic treatment of KS has changed notably in recent years thanks to the introduction of HAART<sup>4,5</sup> and liposomal anthracyclines<sup>6-8</sup>. Before that time, the treatments of choice were interferon alpha and conventional chemotherapy<sup>9-12</sup>. HAART has led to a drastic decrease in KS incidence<sup>13,14</sup> and alone (without specific treatment) can achieve partial or complete remission of tumors in a high percentage of patients with disseminated cutaneous and visceral KS<sup>15-20</sup>. In a retrospective study by Bower et al, treatment of KS was evaluated before and after HAART in a cohort of 78 patients. The authors found that the amount of time before treatment failure was significantly longer after the introduction of HAART (1.7 years compared to 0.5 years, log-rank,  $p < 0.0001$ )<sup>19</sup>. In a second, prospective, study of 39 patients with KS, Dupont et al observed that HAART was more effective against KS even without specific treatment. The authors observed that response to treatment depended on the recovery of the immune system, and found as predictive factors of complete remission at 24 months an increase in the CD4 count to more than  $150 \times 10^6/\text{l}$  from initiation to month 12 (OR: 13.4; CI95%: 2-82) and stage T 0 at inclusion (OR: 7; CI95%: 1.1-42)<sup>20</sup>.

In spite of the therapeutic effect of HAART on KS, some patients experience progression and need specific tumor treatment. Liposomal anthracyclines (daunorubicin and doxorubicin) are cytostatics that are well tolerated and have anti-tumor activity equal to or greater than conventional chemotherapy, making them the treatment of choice for KS<sup>8,21-25</sup>.

Liposomal daunorubicin and liposomal doxorubicin are structurally and pharmacokinetically different. Doxorubicin liposomes are enclosed in a polyethylenglycol cover that makes their destruction by the mononuclear phagocytic system difficult. This means that its half-life is greater than that of liposomal daunorubicin, allowing increased contact between the drug and the tumor cells<sup>24</sup>. These cytostatics have not been compared in the treatment of KS, but these differences may explain the various results observed in clinical trials comparing them with conventional chemotherapy regimens<sup>8,21-25</sup>. For example, in a clinical trial comparing liposomal daunorubicin with polychemotherapy regimen including adriamycin, bleomycin and vincristine (ABV) for the treatment of KS in patients with severe immunodepression and advanced KS, the efficacy of both regimens was similar (approximately 25% in both arms), but tolerance and quality of life were better in the patients treated with liposomal daunorubicin<sup>21</sup>. However, in two clinical trials comparing liposomal doxorubicin with ABV or BV for the treatment of KS in patients similar to those described, doxorubicin was significantly more effective than polychemotherapy regimens (50% compared to 25% in both studies), was better tolerated, and improved quality of life<sup>22,25</sup>. Although a clear correlation has been observed between tumor mass and the viral load of type 8 human Herpes virus (HHV-8) in the cutaneous lesions of KS<sup>25</sup>, but a good correlation has not been found between the decrease in viremia by HHV-8 and the clinical response in patients treated with liposomal doxorubicin<sup>26</sup>.

The recommended doses for treatment of KS are 20 mg/m<sup>2</sup> of liposomal doxorubicin every 3 weeks and 40 mg/m<sup>2</sup> of liposomal daunorubicin every two weeks. The main disadvantage of these drugs is the cost, which is higher than regimens of BV or ABV. In general, tolerance of these drugs is good, with an incidence of adverse effects notably less than that with conventional chemotherapy. The most frequent adverse event is neutropenia, and some patients will require treatment with granulocyte growth factors<sup>21-25</sup>. Fever, vomiting and other adverse effects such as alopecia, stomatitis and cardiotoxicity are less frequent<sup>21-25</sup>. It is worth pointing out that neuropathy, the most frequent com-

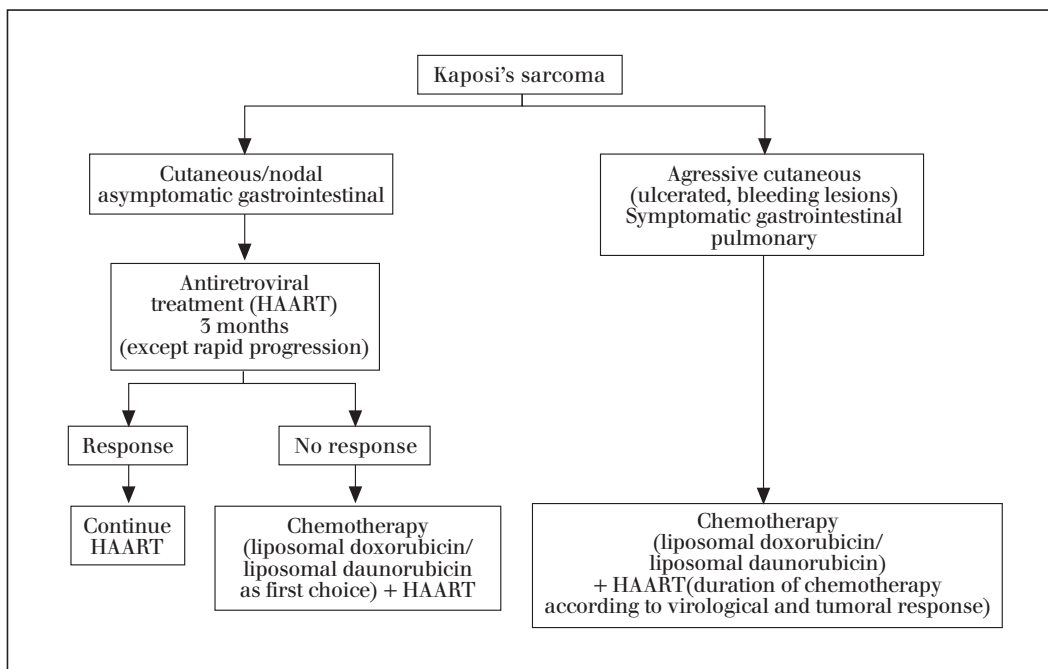
plication in patients receiving vincristine, does not appear with liposomal anthracyclines, allowing its use with antiretroviral regimens that include d4T or ddI.

It has not yet been proven whether patients with AIDS and KS can be treated with HAART alone, or which patients should also receive a liposomal anthracycline. This consensus group recommends immediate treatment with HAART alone in all patients, except in those with particularly virulent forms of KS: large tumor masses, bleeding and/or ulcerating lesions and visceral forms that are life-threatening, such as symptomatic pulmonary involvement or bleeding forms or large masses in the digestive tract or other organs (fig. 1)<sup>27</sup>. When KS progresses in spite of HAART or does not improve after 3 months of treatment, the addition of liposomal anthracyclines is recommended. The duration of treatment with cytostatics (as during the pre-HAART era) is not well established. In general, complete or partial remission is usually obtained after 6 to 8 doses, and at this point it is possible to continue

with HAART alone if over the months the lesions continue to remit (and may disappear completely). Relapses may occur weeks or months after discontinuation of chemotherapy, and in this case chemotherapy should be resumed.

Patients with KS who do not respond to treatment with liposomal anthracyclines can be treated with paclitaxel (taxol), a cytostatic approved by the FDA as second line treatment of KS<sup>28</sup>. The recommended dose is a 3-hour infusion of 135 mg/m<sup>2</sup> every 3 weeks. The most frequent adverse effects of this drug are neutropenia, alopecia, and vomiting.

There are other type of KS treatment being investigated such as vinorelbine (a new semisynthetic vinca alkaloid), retinoic acid-derived angiogenesis inhibitors, thalidomide, and chorionic gonadotrophin<sup>29-31</sup>. It has been suggested that treatment with foscarnet or gancyclovir (given their anti HHV-8 activity) could prevent the appearance of KS in patients infected by HIV. However, the therapeutic efficacy of these antiviral medications against KS has not yet been demonstrated<sup>32</sup>.



**Figure 1.** Therapeutic algorithm of AIDS-associated Kaposi sarcoma<sup>28</sup>. This algorithm was agreed upon at an experts' meeting in Barcelona in June 1998. (Coordinators: Dr. J. González Lahoz and D. Podzamczar. Participants: M. Alsina, J. Berenguer, F. Bolao, C. Camps, B. Clotet, J. Pedreira, J. Rodríguez Piñeiro, R. Rubio, P. Saballs and E. Valencia).

## Topical treatment of muco-cutaneous Kaposi sarcoma

Although AIDS-associated KS is generally a disseminated disease and its treatment systemic, different types of topical treatment are of interest<sup>53</sup>.

The objective of topical treatment in most cases is not curative but palliative, and is an attempt to correct aesthetic problems or those stemming from the edema, ulceration, or lesion volume<sup>54</sup>. Although local therapy may be the only therapy used (isolated lesions or systemic intolerance to chemotherapy), it is also used in combination with other systemic treatment regimens to try to control specific lesions, especially in the first months after initiation HAART while awaiting a favorable immunological response.

Therapeutic response is affected by the age of the lesion (early lesions respond better than fibrous lesions), its growth cycle, and the general immunological condition of the patient. Residual changes in pigmentation occur frequently.

There are no established regimens for this part of KS treatment. Table 1 shows recommendations for evaluating the usefulness of different topical therapy. Cryotherapy, with liquid nitrogen in repeated sessions every 10-21 days, has been widely used. Excision by surgical resection or electrocoagulation of the base is useful for isolated lesions, but the lesions frequently recur rapidly.

Radiotherapy, which generally uses orthovoltage and medium depth techniques for superficial skin and mucous lesions, has the advantage of being fast and resulting in fewer relapses medium-term than intralesional treatment, the main disadvantage being the possibility of acute radiodermatitis that is very symptomatic in these patients (especially in the oral mucosa, necessitating the use of lower doses or contact radiotherapy techniques)<sup>35,36</sup>.

The intralesional route is taken for chemotherapy drugs and interferon alpha. The only broad experience with the first group is with vinblastine<sup>37</sup>, generally used with or following anesthetics, in several sessions 2-4 weeks apart<sup>38</sup>. Isolated studies have stressed the significant therapeutic effects with intralesional sclerotherapy, particularly in the oral cavity<sup>39</sup>.

In 1999, the FDA authorized the use of a topical retinoid for the KS epidemic: 9-cis-re-

TABLE 1. Local therapy in Kaposi sarcoma

Types of local therapy	Indications
None	Asymptomatic lesions that are slowly progressive and without esthetic repercussions
Cryotherapy	Isolated small or medium-sized cutaneous-mucosal lesions and located in cartilaginous locations (eyelids)
Surgery	Pedunculated and tuberoso cutaneous lesions
Radiotherapy	Large aggressive cutaneous lesions (ulceration, pain) or lesions that progress with lymphedema (frequent in perinasal area), and lesions on the face or feet (painful soles); Similar lesions of the genital or oral mucosa (more controversial due to side-effects), and nodal lesions (inguinal with lymphedema of the lower limbs). Also indicated for symptomatic lesions of the digestive tract and lungs.
Intralesional	Isolated cutaneous medium-sized lesions, with a deep nodular component. Also used in oral mucosa.
Topical retinoid	«Home» treatment of multiple cutaneous lesions that are not very aggressive.
Laser	Superficial cutaneous lesions. With esthetic repercussions

tinoid acid or alitretinoin applied twice or more daily for months. Its mechanism of action is believed to be a decrease in the expression of growth factors such as IL-6. It is easy to use<sup>40</sup> and is considered a good complement to systemic therapies such as HAART<sup>37,41</sup>, although the response is late and it is expensive. This and recurrences are the main drawbacks of color-pulsed and Neodim-Yag laser treatment for KS

## Pre-invasive cervical lesions and cervical cancer in HIV-infected women

### Introduction

The true dimensions of the impact of HIV on the field of gynecology has begun to draw attention. Cancer of the cervix and its precursor lesions, squamous infraepithelial lesions (SIL), are the most important gynecological manifestations in HIV-infected women. SIL are divided into low grade SIL (or CIN I) and high grade SIL (or CIN II or III). HIV-positive women are at greater risk of developing both cancer of the cervix and SIL compared to HIV-negative women<sup>42,45</sup>. In fact, in 1993,

cancer of the cervix was considered an AIDS-defining disease<sup>44</sup>. At present, the prevalence of cervical cancer and/or SIL in HIV-infected women is 20% to 43%<sup>45,46</sup>. Prevalence is increasing with the longer patient survival rates thanks to HAART, which allows the appearance long-term complications that did not present in the past, as in the case of cervical lesions and their progression to invasive carcinoma<sup>47</sup>.

The natural history of pre-malignant and malignant lesions of the cervix is altered in HIV-infected patients, and progresses more quickly to disease, is more aggressive, has more persistent lesions, a higher number of recurrences after treatment, and a shorter period of time before recurrences<sup>48,49</sup>.

Given the close relationship between SIL and cancer of the cervix, it is wise to carry out serology testing to rule out HIV in women presenting with pre-malignant or malignant pathology.

### **Pathogenesis**

Cervical infection by the human papilloma virus (HPV) is the most significant risk factor in the development of SIL and cancer of the cervix<sup>46,50,51</sup>. The histological changes associated with HPV (koilocytosis, multinucleation, and increased mitosis) are indistinguishable from those of SIL<sup>50</sup>. HPV-associated oncogenesis stems from an change in the expression of viral proteins E6 and E7 that produce inactivation of tumor cell suppressor genes such as retinoblastoma (RB) and p53, leading to an alteration of the cellular cycle, with defective DNA repair and a malignant transformation of the cervical cells<sup>52</sup>. Immunosuppression favors both cervical infection by HPV with oncogenic genotypes, mainly subtypes 16, 18 and 31, and their clinical expression<sup>45,51</sup>.

HIV infection is associated with a high prevalence of HPV infection, especially of oncogenic genotypes<sup>50,51,53,54</sup>. Similarly, HPV infection is more common in HIV-infected patients<sup>55</sup>. HIV affects acceleration of infection by oncogenic HPV subtypes<sup>47</sup>. The presence of HIV-infected cells and changes in local immunity induced by same may affect the development of SIL of the cervical cells with latent HPV infection<sup>46</sup>. However, direct molecular interaction between HIV and HPV seems improbable as HIV infection of cervical or vaginal cells has not been observed<sup>51</sup>.

The degree of immunosuppression is related to the appearance and severity of SIL and cervical cancer in HIV-positive patients<sup>47,55</sup>. Similarly, high CD4 lymphocyte counts are associated with latent HPV infections, whereas clinical manifestations become obvious as the CD4 lymphocyte count decreases<sup>47</sup>.

Since the introduction of HAART, a regression in cervical lesions has been observed, but HPV persists with the same viral genotypes<sup>46</sup>. This suggests that there are other factors that involved in the development of cervical lesions, and HIV may even be an independent factor<sup>46,51,56</sup>.

## **Diagnosis**

### **Pre-cancerous lesions**

#### *Histopatology*

The diagnostic method for screening pre-cancerous lesions of the cervix in HIV-infected patients is not yet clear. In 1995, the Centers for Disease Control (CDC) recommended the performance of an annual smear in HIV-infected patients who had two previous normal consecutive smears within six months between<sup>57</sup>. However, many physicians recommend a smear every six months in these patients because of the frequency of false negative results, as the alteration or inflammation of the surface of cervical mucosa cells as the result of other sexually transmitted diseases can make it difficult to identify dysplastic cells<sup>58-60</sup>. Following the recommendations of the United States Health Authorities, the Papanicolau test should be performed every 6 months initially and annually after two consecutive negative results have been obtained.<sup>61</sup>

#### *Colposcopy*

Colposcopy should be performed when severe inflammation is present in the smear with(out) atypia, moderate atypia, or the presence of ASCUS (atypical squamous cells of uncertain significance) due to the frequent association of these lesions with SIL<sup>62,63</sup>. Given the frequent cervical mucosa changes, with inflammatory signs in a significant number of patients infected by HIV, some authors recommend the performance of an annual colposcopy together with the smear<sup>58-60</sup>.

#### *HPV*

The convenience of including tests to detect HPV infection has not been clearly established.

According to some authors, there are a large number of false negative results with the Papanicolaou test, supporting systematic performance of PCR to rule out HPV infection<sup>51,64,65</sup>. Other techniques used to detect HPV DNA are Hybrid Capture I and Southern Blot hybridization, often associated with PCR<sup>46,51,66</sup>.

### Biopsy

Histopathology must be determined for every suspicious macroscopic lesion, regardless of smear results<sup>67</sup>. Biopsies must also be performed of the so-called «major abnormal lesions» diagnosed by colposcopy, such as the mosaic, thick point, and wide areas of leukoplakia with spicated edges<sup>51</sup>. The appearance of a low grade SIL in the smear is an indication for biopsy<sup>51,67</sup>. Histological material can be obtained using three techniques:

1. *Colposcope-directed punch biopsy*. Often, a less serious lesion than that which really exists is obtained<sup>68</sup>.
2. *Excision of the entire transformation area with a dyathermic loop*. This technique is recommended as a replacement for the punch biopsy. In many

cases, it has the advantage that treatment can be carried out concurrently with diagnosis<sup>68,69</sup>.

3. *Endocervical curettage*. Microcolposcopy. Indicated when the smear reveals cylindrical atypical cells or when colposcopy does not allow visualization of the entire transformation zone<sup>67</sup>.

### Infrared spectroscopy

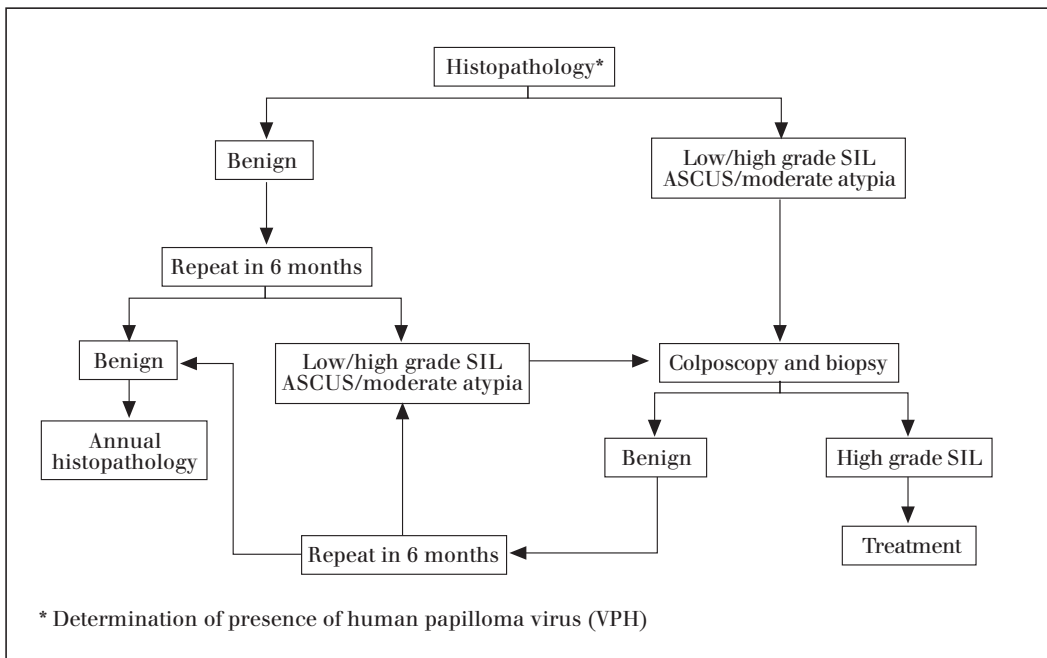
A new technique with great potential for the diagnosis of cervical cancer involving the study of cervical samples. Its use as a diagnostic method is still under discussion<sup>70</sup>.

### Anogenital exploration

The high incidence of concomitant cancers of the vulva, vagina and anus makes performance of an exhaustive examination of this region at each visit essential<sup>71,72</sup>. Figure 2 summarizes the most accepted diagnostic follow-up parameters.

### Invasive carcinoma of the cervix

Invasive carcinoma of the cervix, unlike other pre-cancerous lesions, leads to clinical symptoms. The most frequent clinical symptoms



**Figure 2.** Algorithm for the diagnosis and follow-up of pre-malignant cervical pathologies in HIV-infected patients. SIL: squamous intraepithelial lesions of the cervix, ASCUS: atypical squamous cells of uncertain significance.

are intermittent vaginal bleeding, bleeding during intercourse and increased and foul-smelling vaginal discharge. Pelvic, lumbosacral, or lower limb pain, as well as changes in micturition or stool, are more frequently associated with advanced disease<sup>50</sup>.

Very few cases of invasive carcinoma are detected via routine smear testing. The most characteristic finding is the presence of a cervical mass, which bleeds on touch and is friable with or without extension to adjacent structures. The presence of inguinal adenopathies and leg edema appears to indicate metastasis<sup>50</sup>. Metastases occur more frequently and rapidly in HIV-infected patients than in seronegative patients, and appear in unusual sites<sup>73,74</sup>. When a cervical lesion is suspected of being malignant, biopsy is the best method for diagnosing cancer of the cervix<sup>50</sup>.

## Treatment

### Pre-cancerous lesions

#### *Excisional or ablative treatment*

These include cryosurgery, laser ablation, conization with cold scalpel and conization with diathermia (LEEP)<sup>50</sup>. These techniques are successful in 80% to 90% of seronegative patients<sup>50</sup>. However, given the rapid and aggressive course of lesions in HIV-infected patients, the results are less satisfactory, and the lesion persists or recurs in 39% to 62% of cases<sup>75-78</sup>. Therefore, after ablation or excision, colposcopy and smear are recommended every three months<sup>50</sup>. Recurrence or persistence of precancerous lesions is closely related to the degree of immunosuppression<sup>45,51,84</sup>.

#### *Medical treatment*

Medical therapy as primary or adjuvant treatment has been evaluated by several investigators.

1. *Oral betakarotenes and intralesional or systemic interferon*. Their use has not resulted in significant benefits in the treatment of SIL<sup>79, 80</sup>.
2. *Retinoids*. Have a favorable response in 33% to 90% of patients and no disease progression. At present, oral isotretinoin is being tried as primary therapy in low grade SIL, and topical retinoic acid in high grade SIL<sup>50, 81</sup>.

3. *5-fluoruracil (5-FU)*. Its application in the form of vaginal cream after excision or ablation has been shown to reduce the number of recurrences of SIL as well as increasing (note: should this be decreasing?) their duration<sup>82</sup>. The regimen used is 5% 5-FU at 2 grams twice weekly for six months<sup>82</sup>.
4. *HAART*. Its application in HIV-infected pregnant women is relatively recent, so the results on SIL are limited. It appears that patients treated for 5 months with HAART after cervical excision have a lower number of recurrences than those treated with excision only<sup>46,83</sup>. However, the presence of infection by HPV is not eliminated and the same viral genotypes are identified after treatment, suggesting that other factors influence the development of cervical lesions in addition to HPV<sup>46</sup>.

### Treatment of HPV

The recognition of latent viral infections as a cause of cancer opens a new therapeutic approach<sup>84</sup>. The use of new peptide vaccines, both as prophylaxis and therapy, is now in the first sta-

TABLE 2. FIGO classification of cancer of the cervix (Federación Internacional de Ginecología y Obstetricia). 1995

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<b>Stage I.</b> Tumor limited to the neck of the uterus
<i>Stage Ia.</i> Invasive cancer only identified microscopically
<i>Stage Ia1.</i> Deep stromal invasion less than 5 mm in depth. Width less than 7 mm.
<i>Stage Ia2.</i> Deep invasion between 5 and 5 mm in depth. Width less than 7 mm.
<i>Stage Ib.</i> Clinical lesions confined to the cervix or preclinical lesions greater than stage Ia
<i>Stage Ib1.</i> Infiltrating tumor less than or equal to 4 cm in size
<i>Stage Ib2.</i> Infiltrating tumor more than 4 cm in size
<b>Stage II.</b> Tumor beyond the neck, but not reaching the pelvic wall and/or extension to the vagina without reaching the lower third
<i>Stage IIa.</i> Affects the vagina without reaching the lower third
<i>Stage IIb.</i> Affects the parametrium without reaching the pelvic wall
<b>Stage III.</b> Tumor extended to 1st lower third of the vagina and pelvic wall
<i>Stage IIIa.</i> Extension to the lower third of the vagina, but not to the pelvic wall
<i>Stage IIIb.</i> Extension to the pelvic wall. If there is hydronephrosis or renal annulation, even if the tumor is included in stages I or II, it is catalogued as IIIb
<b>Stage IV.</b> Extension outside the pelvis, or involvement of vesicle or rectal mucosa*
<i>Stage IVa.</i> Extension to neighboring pelvic organs
<i>Stage IVb.</i> Extension to distant organs

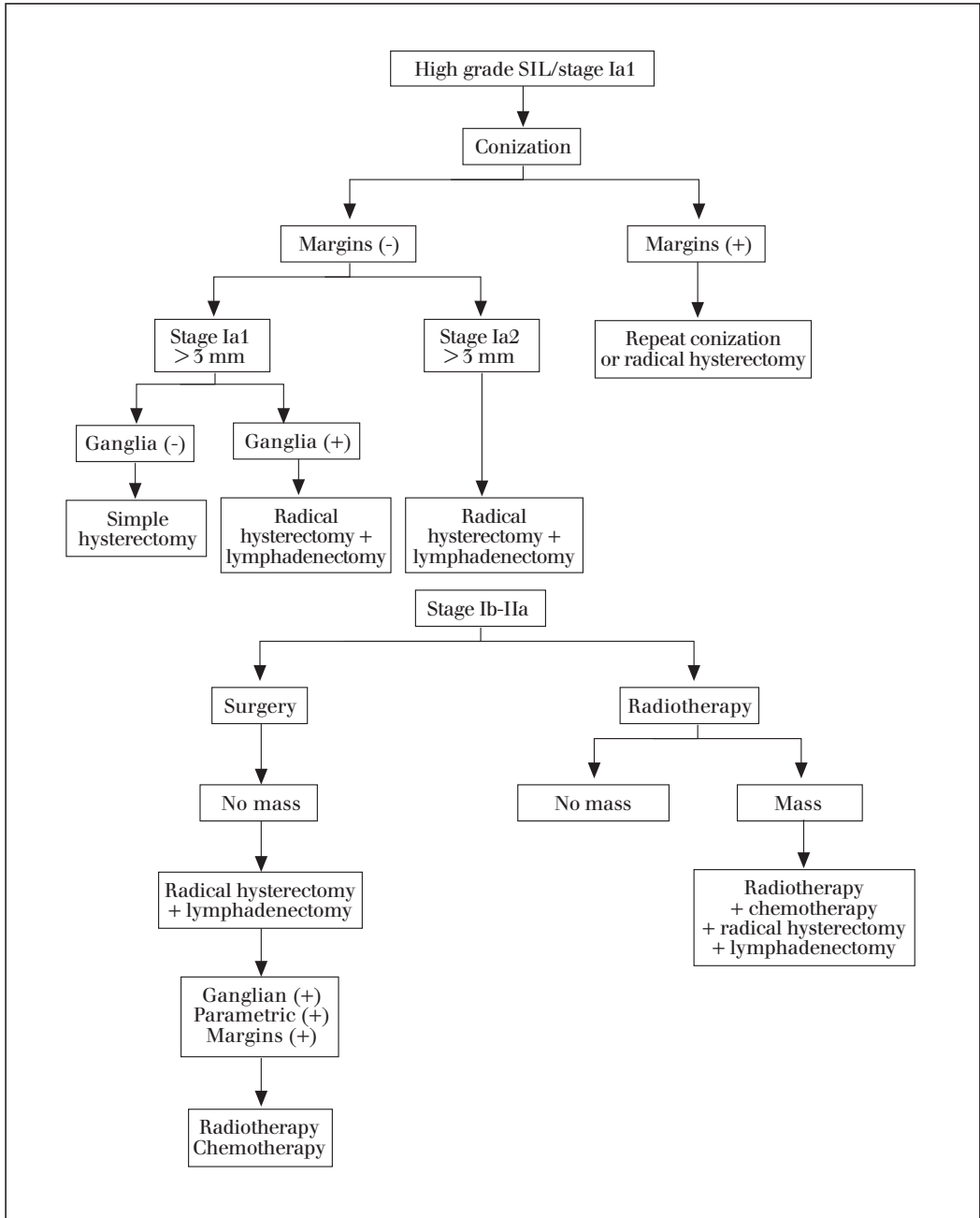
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\* Existence of vesicle edema does not allow it to be included in stage IV.

ges of development<sup>85</sup>. With regard to pre-existing HPV infection, tests are being performed to reinforce cellular immune response to the virus as the main strategy for its eradication.

**Cancer of the cervix**

HIV-infected patients who develop cancer of the cervix are younger than seronegative women and are less immunosuppressed than



**Figure 3.** Algorithm of treatment of squamous intraepithelial lesions of the cervix and cancer of the cervix. SIL: squamous intraepithelial lesions of the cervix.

other patients with another AIDS-defining disease<sup>50</sup>. These characteristics necessitate a different approach for treatment of cancer of the cervix in HIV-infected patients and from the outset should be more aggressive.

### Surgery

1. *Conization with dyathermic loop*. For microinvasive lesions less than 3 mm in depth or stage IA1 of IFGO (International Federation of Gynecology and Obstetrics) in women who want to have children.
2. *Total simple hysterectomy*. The method of choice for most cases, maintaining anexa and vaginal function.
3. *Radical hysterectomy*. In infiltrative or large tumors, stages IB and IIA of the IFGO (for IFGO classification see table 2). Anexa, the upper third of the vagina, periuterine tissues including lymphatic drainage collectors and regional ganglia are removed.

### Radiotherapy

The most widely used treatment is external radiotherapy by irradiating the entire pelvis and lumbo-aortic region, followed by intracavitary radiotherapy with iridium or cesium implants<sup>50</sup>. Radiotherapy can be used in stages IB and IIA of the IFGO as the sole treatment, although in most cases it is used in conjunction with surgery. The most frequent complications are intestinal obstruction, vesicle fistulas, and ovary damage<sup>50</sup>.

### Chemotherapy

Chemotherapy in cancer of the cervix is usually used alone as palliative treatment in cases of relapse or advanced illness, or in combination with other therapies as curative treatment. The use of cisplatin as the sole chemotherapy agent in cancer of the cervix has shown modest anti-tumor activity with responses in 20% to 25% of patients<sup>86</sup>. In cases of advanced cancer of the cervix in HIV-infected patients, the response to chemotherapy has been minimal<sup>50</sup>. Sideeffects from chemotherapy such as myelosuppression and neuropathy deteriorate the state of HIV-infected patients; therefore it should only be considered after taking into account the few benefits obtained versus the adverse effects on survival of these patients. Figure 3 summarizes the most accepted treatment.

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