INTERNATIONAL SOCIETY FOR THE STUDY OF VULVOVAGINAL DISEASE

A Message From The President

First of all, I would like to thank everyone for having given me the great honor and opportunity of leading our Society.

As President I aspire to be a guide for our members, I will focus more on coordination rather than on direction, taking into account the suggestions and proposals of each and every member of the Society.

Nothing is possible if we work alone! Teamwork is what will make us reach our goals, especially what will make our dear Society grow, allowing our knowledge to reach future generations all over the world.

Working together will make the dream come true.

In any organization or society like ours, teamwork is of paramount importance and constitutes the key to success.

Our Society has always displayed good team spirit through management and consensus committees. Our main idea is to reinforce work in this direction.

Our motto ***"Working together to reveal the truth of Vulvovaginal disease"*** highlights the need for joint work.

In our newsletters we will share with you why team work is essential and we will also define the following:

- Teamwork: definition
- Why teamwork matters?

- Characteristics and requirements of teamwork
- Advantages and disadvantages
- Differences between teamwork and group work
- Why teamwork fails?

TEAMWORK

- **Definition**

Teamwork can be defined as that activity that, in order to be achieved, requires the participation of different people. This implies a joint need to share skills and knowledge as well as a trusting relationship that allows delegating part of our own tasks to a teammate, knowing for sure that he or she will carry out the task assigned.

Teamwork gives the opportunity for personal growth and constitutes a true social success. It makes personal development easier by helping others through commitment, integration and tolerance.

The team generates a sense of belonging and a feeling of satisfaction regarding tasks, projects and values. The team allows us to learn and to enrich ourselves. Besides, it also facilitates achievement of objectives.

- **Why teamwork matters?**

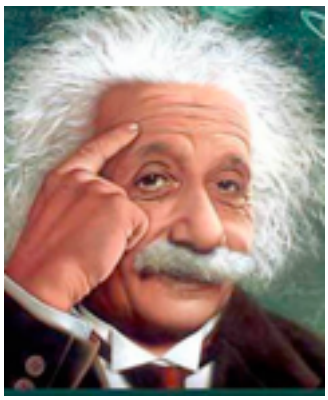
Privileging individual work and seeking personal benefits are not uncommon in our Society. This is the reason why it is difficult for us to adjust and especially to commit ourselves to team work.

Besides, in order to work in a team, it is essential to commit ourselves to achieving the goals set. This involves giving up the individualistic habit of believing only in the results of personal effort. It requires trust in the teammates' capabilities. Teamwork also implies taking for granted that our teammates are as committed as we are to achieving the objectives of the organization and that they work efficiently to attain these objectives.

"Try not to become a man of success, but rather try to become a man of value."

-ALBERT EINSTEIN

In a work team, communication should be fluent, spontaneous and natural. Feelings should be respectfully expressed regarding the privacy and prestige of each and every member of the team. Differences in style, in the way to communicate and in personal approaches should not constitute an obstacle but an opportunity of developing team unity.



A team is not a sum of individuals; it is a dynamic and changing reality of the members' expressions.

All the team members are fully convinced that goals can be achieved more easily with joint rather than with individual work.

When working with people from other cultures, with other needs, interests, tastes and traditions, it is essential to be very creative in order to satisfy them all. This happens in our Society, the ISSVD. Therefore, let's exchange ideas, ALL TOGETHER!

"Good teams become great teams when the members trust each other enough to surrender the "me" for the "we"

We invite you to enjoy a personalized message from President, Dra. Claudia Marchitelli via YouTube

ISSVD President´s message in English
https://www.youtube.com/watch?v=6jqmFX6QeFg

Mensaje de la Presidente de la ISSVD en Español
https://www.youtube.com/watch?v=Y2uG8UqUGYw

The 2015 ISSVD TERMINOLOGY OF VULVAR SQUAMOUS INTRAEPITHELIAL LESIONS

The terminology that was passed at the XXIII World Congress in New York will be Published in Journal of Lower Genital Tract Disease January 2016 issue and is available at http://issvd.org/wp-content/uploads/2015/09/2015-ISSVD-VIN-terminology-for-the-website-v5.pdf

UPDATE OF HSIL OF THE VULVA AND DVIN
by: Mario Preti, MD

Vulvar Squamous Intraepithelial Lesions

High grade squamous intraepithelial lesion [Vulvar HSIL] and Vulvar Intraepithelial neoplasia, differentiated-type [DVIN].

The recent New York ISSVD Congress and the last published articles on Vulvar Squamous Intraepithelial Lesions allow us to make some considerations about Vulvar HSIL and Vulvar Intraepithelial neoplasia [VIN], differentiated-type [DVIN]. These diseases are attracting more and more attention of clinicians, pathologists and researchers.

DIAGNOSIS

The XXIII ISSVD World Congress pointed out the need of correct Vulvar Squamous Intraepithelial Lesions diagnosis. Allbritton and co-workers showed how frequently clinicians consider HSIL prior to biopsy. In 49% of the 127 patients examined there was no documented suspicion of malignancy (HSIL, squamous cell carcinoma (SCC), basal cell carcinoma or melanoma) before the biopsy. In patients younger than 50 years, only 37% of the biopsies included a clinical suspicion of HPV or SCC.

And if dermatology providers often fail to consider the diagnosis of HSIL in pigmented genital lesions, Preti and Micheletti demonstrated that among 240 diagnoses of squamous intraepithelial lesions of the vulva on biopsy (88,7% HSIL of the vulva and 11,3% DVIN) invasive carcinoma was diagnosed in 16,7% of lesions submitted to excisional treatment: 19/27 DVIN (70,4%) and 21/213 HSIL (9,8%). In HSIL multivariate analysis showed a risk of occult invasive cancer detection increased for patients in the highest tertile of age ($P = 0.008$), for patients with a lesion ≥20 mm in size ($P = 0.013$) and with clitoral involvement ($P = 0.000$)

Jason Reutter et al. from Duke University, Durham, NC. sought to recognize the working diagnostic criteria for DVIN amongst expert pathologists in the field. Only basal layer atypia was considered diagnostically essential by consensus. Additional criteria that strongly support the diagnosis include: changes affecting the basal layer (e.g. presence of hyperchromasia and mitoses) and abundant eosinophilic keratinocytic cytoplasm. There was not a consensus on any ancillary study to confirm the diagnosis.

These studies demonstrated us how important is to consider Vulvar Squamous Intraepithelial Lesions among differential diagnosis and **the need of appropriate biopsy and histopathological diagnosis before treatment.** Knowledge of patient and disease characteristics assist the decision making for biopsy and treatment of disease.

In last year relevant studies reported genetic alterations (somatic mutations, allelic imbalances, loss of heterozygosity, copy number changes) and epigenetic changes (hypomethylation and hypermethylation, microsatellite instability, and chromatin, histone, and posttranscriptional modifications) that play a role in vulvar carcinogenesis and may provide valuable insight into its etiology.

In HPV-negative VSCC, mutations are often found in the tumor suppressor gene *TP53*. *TP53* mutations are thought to be an early event in the development of VSCC because they are also found in DVIN and LS lesions. Other mutations have been described in VSCC and its

precursor lesions, including mutations in the tumor suppressor genes *PTEN* and*CDKN2A*, allelic imbalances or copy number alterations.

In addition to genetic mutations, epigenetic changes (changes in gene expression without changes in the DNA sequence) may also play a role in the development of VSCC. Among epigenetic changes, the best known epigenetic change is hypermethylation of CpG islands in the promoter regions of tumor suppressor genes, causing inactivation of the gene. In vulvar cancer hypermethylation of the promoters of *RASSF2A*, *MGMT,* and *TSP1* has been described.

Jones RW, Rowan DM and Stewart AW (2005) Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women Obstet Gynecol 106(6) 1319–1326 DOI: 10.1097/01.AOG.0000187301.76283.7f PMID: 16319258

THERAPY

If diagnosis is the first step approaching patients with Vulvar Squamous Intraepithelial Lesions, considering therapy we remember the Workshop on intraepithelial neoplasia of the vulva held at the 2009 ISSVD World Congress in Edinburgh, Scotland. Debra Heller et al. wrote: “The goal is to provide optimum therapy while causing the least tissue destruction. The recent change in the classification of vulvar intraepithelial neoplasia and the newer therapeutic modalities have been areas where there is a role for education and discussion”.

After 6 years we have the new ISSVD classification, as detailed elsewhere in this Newsletter, and the same goal: “To provide optimum therapy while causing the least tissue destruction”. In fact the ideal treatment of Vulvar Squamous Intraepithelial Lesions is primarily based on the prevention of invasive development, maintenance of urogenital anatomy and functionality, treatment of symptoms and minimizing complications.

The last published Cochrane review on “Surgical interventions for high-grade vulval intraepithelial neoplasia” by Kaushik et al. stated that there was insufficient evidence to conclude that either surgical technique is superior over the other. In the meantime another Cochrane review on “Medical interventions for high-grade vulval intraepithelial neoplasia” underlined the high morbidity and relapse rates associated with surgical interventions and medical therapy as promising way to preserve vulvar anatomy after exclusion the presence of stromal invasion with accurate biopsies. Specifically Tristam et al published a multicentre, open-label, randomised, phase 2 trial on activity, safety, and feasibility of the nucleotide analogue Cidofovir and topical Imiquimod for treatment of HSIL of the vulva with good responses recorded with both drugs, even if the long-term efficacy of

Cidofovir remains to be proven. Furthermore the therapeutic effect of Cidofovir seems to be both antiviral and cytotoxic, which could potentially benefit immunocompromised patients. The Authors concluded that in the future, topical treatments could evolve to become the treatment of choice for people with HSIL of the vulva, with cold- knife resection and laser vaporisation reserved for patients not responding to initial treatment.
Even if no topical drug is currently approved for treatment of Vulvar Squamous Intraepithelial Lesions, to consider medical therapy for HSIL of the vulva leads us to reflect on the role of the immune system.

As HPV-related malignancies, HSIL of the vulva are associated with persistent HPV infection. In 90% of cases, the immune system is capable of clearing a transient HPV infection within 2 years. The host immune response is of crucial importance in determining clearance or persistence of both HPV infections and HPV-related VIN. The longer the infection persists, the longer E6 and E7 can interfere with important control mechanisms of the cell cycle.

This is clearly seen in immune-compromised patients where the malignant potential of HSIL of the vulva is 50-fold higher compared to the general population.

Very interesting studies on failure of the immune system to produce an effective response to high-risk HPV (related to both viral persistence and various host factors) are reported by van Esch and co-workers.

Waiting for strategies aiming to reinforce the immune response to tumour-specific antigens, E6 and E7, to prevent HPV-related cancers we have immune-response modifiers like Imiquimod: in vivo studies have demonstrated that Imiquimod is a potent inducer of interferon (INF) α, tumour necrosis factor α, and interleukin-6. In animal models, Imiquimod has demonstrated potent antiviral and antitumour effects. Imiquimod acts through a toll-like receptor (TLR7) inducing T cells activation and proinflammatory cytokines release. The studies of van Seters and Terlou showed an effective long term efficacy of Imiquimod, since Vulvar HSIL recurred in only one case of the complete respondents.

The clinical efficacy of Imiquimod is connected to induced clearance of HPV and associated with the normalization of immune cell count in HSIL of the vulva. Many different pre-existing conditions can determine failure of patients' responsiveness to immunotherapy: lesion size, lack of immune infiltration, CD4+ or CD8+ HPV-specific T-cell response, defects in HLA class I expression, IFNγ-associated response, genes of antigen presentation pathway, genes involved in T-cell migration and in chemo or cytokine production.

Also the infiltration of myeloid cells HSIL of the vulva may influence microenvironment and responses to immunotherapy as demonstrated by van Esch. HSIL of the vulva progression is characterized by increases in intraepithelial and stromal M1 and M2 macrophages and by dense intraepithelial infiltration by CD141 macrophages. Dense CD141 macrophage infiltration is associated with a significantly increased risk of recurrence, indicating that it is an independent prognostic factor for disease recurrence.

An increased comprehension of the immunological environment that can be found in HSIL of the vulva might help to better understand the conditions that favour the persistence of HPV and the development of HSIL of the vulva and its potential oncogenic transformation to IVC. It might also help to define immunological markers that can predict responsiveness to immunotherapy. Therefore HSIL of the vulva and recurrent lesions may represent the harder challenge for immunotherapies.

PREVENTION

The recent analysis of over 2,000 intraepithelial and invasive lesions of the vulva made by the HPV VVAP study group detected HPV-DNA in 86.7% of the Vulvar Squamous Intraepithelial Lesions cases. HPV 16 was the commonest genotype (77.3%) detected in HSIL of the vulva, followed by HPV 33 (10.6%) and HPV18 (2.5%).

HPV prophylactic vaccination has demonstrated to be effective in preventing HSIL of the vulva. The vaccine efficacy against HPV 16- and/or HPV 18-related HSIL of the vulva is highest in the HPV-naive population, with a 94.9% efficacy. Although prevention of IVC was not demonstrated, prevention of premalignant HSIL of the vulva may anticipate a reduction of rates of HPV-related IVC. The US Food and Drug Administration has recently approved a recombinant 9-valent HPV vaccine for the prevention of cervical, vaginal, vulvar and anal cancer cases caused by HPVs 16/18/31/33/45/52/58 and for the prevention of genital warts caused by HPVs 6/11. Several trials have assessed suitable safety, tolerability and immunogenicity profiles of the 9-valent HPV vaccine In XXIII ISSVD Congress Elmar Joura reported data on the end of study efficacy for Vulvovaginal Ddisease of 9-valent HPV L1 Virus-like Particle vaccine in 16-26 year old women. 12,021 women were eligible for analysis. Efficacy against vulvovaginal disease caused by HPV 6/11/16/18 was equal to qHPV vaccine (against HPV 6/11/16/18). Efficacy against HPV 31/33/45/52/58-related Vulvar and Vaginal Squamous Intraepithelial Lesions (any grade) in the primary analysis was 94.4% (95% CI: 67.7, 99.7). No case of vulvovaginal HSIL related to the 5 new types was observed in the 9vHPV vaccine group and 3 cases were observed in the qHPV vaccine group.

This until yesterday. Today and tomorrow the increasing amount of interest and research for Vulvar Squamous Intraepithelial Lesions will increase more and more results in the diagnosis of this disease with rapid benefits for affected patients.

PaavonenJetal(2009)Efficacyofhumanpapillomavirus(HPV)-16/18AS04-adjuvantedvaccineagainstcervicalinfectionand precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women Lancet 374 301–314 DOI: 10.1016/S0140-6736(09)61248-4 PMID: 19586656

Brown DR et al (2009) The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16–26 years J Infect Dis 199 926–935 DOI: 10.1086/597307 PMID: 19236279

Einstein MH et al (2011) Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18–45 years Hum Vaccin 7(12) 1359–1373 DOI: 10.4161/hv.7.12.18282 PMID: 22048172 PMCID: 3338933

Kemp TJ et al (2011) HPV16/18 L1 VLP vaccine induces cross-neutralizing antibodies that may mediate crossprotection Vaccine 29 2011–2014 DOI: 10.1016/j.vaccine.2011.01.001 PMID: 21241731 PMCID: 3046309

QUESTION AND ANSWERS FROM THE EXPERTS ABOUT THE TERMINOLOGY CHANGES

(SHARED WITH PERMISSION)

I am hoping to get some guidance from you regarding the ISSVD Vulvar Squamous Lesion terminology changes. I am a practicing pathologist who will be guiding the rest of my group with this conversion.

1. Low Grade Squamous Intraepithelial Lesion (formerly condyloma/ HPV effect)
2. High Grade Squamous Intraepithelial Lesion (formerly VIN, usual type)
3. Intraepithelial Neoplasia, Differentiated type

With respect to categories 2 and 3, how does one distinguish "HPV associated" Usual Type from “Non-HPV associated" Differentiated Type on a small biopsy? (HPV testing by in-situ hybridization on biopsy material is not extremely sensitive at this time. Do you advocate testing all of these for p16 by immunohistochemistry? Although, I would hate to hang my hat on the p16 as the sole determiner that the high grade lesion was truly HPV-associated. I know that the differentiated type is typically seen in the older patient; however, this is becoming less applicable in our practice.)

Regarding Category 3: Does this imply that it is a high grade lesion only.... High grade is not specifically stated in the terminology table and I am afraid I will get lots of calls on that, if I don't specifically state this.

Are there provisions for the term Carcinoma in-situ? Does one lump all Carcinoma in-situs, whether they be of HPV associated or not, into a single term?

Thank you for your help, Jacqueline Emery, MD

RESPONSE FROM PROFESSOR JACOB BORNSTEIN, CHAIR OF TERMINOLOGY COMMITTEE

Dear Dr. Emery,
Thank you for asking. I wish that more pathologists use the same terminology as the clinicians use. We have not introduced HPV and p16 stain as requirements for diagnosis, into this terminology, because of the same concerns that you raised.

The difference between VIN differentiated and High grade vulvar SIL should be histopathological. We have decided not to use of the term CIS for VIN diff, although this was proposed, as in VIN diff, the atypia can be seen only close to the basal cell layer, and not throughout the epithelium.

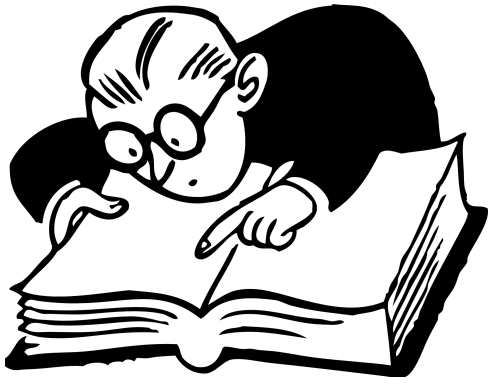
I ask Debbie to forward your question also to Dr. Jason Reuter, the pathologist that served on the terminology committee for further comments.
Regards,
Jacob

RESPONSE FROM JASON REUTTER, PATHOLOGIST ON TERMINOLOGY COMMITTEE

Dr. Emery has some excellent questions!
In regards to the first question. I agree with Dr. Bornstein, although an HPV supportive study (p16 block like positivity or HPV ISH, IHC or PCR positivity) would help to exclude vulvar intrapepithelial neoplasia, differentiated type (DVIN), the diagnosis should rest on morphology. The vast majority of DVIN will only have basal or parabasal layer atypia as well as other supportive features such as enlarged keratinocytes. There is a small reported case series of DVIN mimicking HSIL of the vulva, but these were exceedingly rare and had negative HPV study results, so they were easy to classify in the end (Am J Surg Path 2009; 33:1659-1665).

In regards to the second question: Yes, we are saying DVIN is ALWAYS a high grade lesion. Perhaps following the diagnosis of DVIN with a comment that this is a high grade lesion may be prudent, since the diagnosis, in theory would be a rare one anyway. In the case of equivocal lesions that are difficult to classify precisely as DVIN, one should consider a descriptive term and convey to the clinician that this might either be a benign, reactive process or DVIN rather than designating these lesions as "low grade" and giving the patient and clinician a false sense of security.

I agree with Dr. Bornstein's comment regarding the last set of questions. Another reason not to lump everything under the term "carcinoma in situ" would be that DVIN is much more likely to be associated with invasive cancer than HSIL of the vulva and so, at least in terms of prognosis, it would be better to separate them.



SUMMARY OF THE XXIII WORLD CONGRESS

Thank you to Ione Bissonnette for taking the time to write the summary of the World Congress. It can be read at http://newyork.issvd.org/wp-content/uploads/2015/12/ISSVD-WORLD-CONGRESS-SUMMARY.pdf

COMMITTEES 2015-2017

Thank you to all ISSVD Members/Fellows who have volunteered to serve on committees for the 2015-2017 term. The committees have been updated and posted on the website. Any members/fellows interested in serving on a committee who was not in New York to sign up, please contact the chair of the committee or Debbie Roepe at executive.director@issvd.org to indicate your interest. Committees may be viewed at http://issvd.org/wp-content/uploads/2015/11/Committees2015_17_UPDATEDOctober.pdf

DR. JEFF ANDREWS REPRESENTS ISSVD AT FDA WORKSHOP

On November 10, 2015, The FDA convened a workshop on use of lower-dose vaginal estrogen used to treat Vulvovaginal Atrophy arising from concerns raised during the 2013 Annual Meeting of the North American Menopause Society. A summary of that workshop may be viewed at https://speakingofwomenshealth.com/news/nams-leaders-request-labeling-change-for-low-dose-vaginal-estrogen-for-vulvovaginal-atrophy

CLICK TO RENEW ISSVD MEMBERSHIP DUE BY JANUARY 25, 2015.

OR Click here to download an invoice: http://issvd.org/wp-content/uploads/2015/12/2016-DUES-STATEMENT-.doc

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Thursday, September 8th will be an optional day of sessions.
Friday, September 9th and Saturday, September 10th will include two full days of postgraduate course work and the abstracts from the North American Scientific Sessions.

More information coming soon.

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