The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions

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Objectives: The impact of terminology for vulvar intraepithelial lesions has been significant over the years, because it has affected diagnosis, treatment, and research. The introduction of the Lower Anogenital Squamous Terminology (LAST) in 2012 raised 2 concerns in relation to vulvar lesions: firstly, the absence of reference to "differentiated vulvar intraepithelial neoplasia" (differentiated VIN) could lead to its being overlooked by health care providers, despite its malignant potential. Secondly, including the term "low-grade squamous intraepithelial lesion" (LSIL) in LAST recreated the potential for overdiagnosis and overtreatment for benign, self-limiting lesions.

Materials and Methods: The International Society for the Study of Vulvovaginal Disease (ISSVD) assigned the terminology committee the task of developing a terminology to take these issues into consideration. The committee reviewed the development of terminology for vulvar SILs with the previous 2 concerns in mind and reviewed several new terminology options.

Results: The final version accepted by the ISSVD contains the following:
•Low-grade SIL of the vulva or vulvar LSIL, encompassing flat condyloma or human papillomavirus effect.
•High-grade SIL or vulvar HSIL (which was termed "vulvar intraepithelial neoplasia usual type" in the 2004 ISSVD terminology).
•Vulvar intraepithelial neoplasia, differentiated type.

Conclusions: The advantage of the new terminology is that it includes all types of vulvar SILs, it provides a solution to the concerns in relation to the application of LAST to vulvar lesion, and it is in accordance with the World Health Organization classification as well as the LAST, creating unity among clinicians and pathologists.

Key Words: vulvar squamous intraepithelial neoplasia, differentiated vulvar intraepithelial neoplasia, low grade squamous intraepithelial lesion, high grade squamous intraepithelial lesion, Lower Anogenital Squamous Terminology

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Members of the ISSVD 2013–2015 terminology committee included Jacob Bornstein MD, MPA (Chairman). The other members are the following: Fabrizio Bogliatto, MD, Tanja G. Bohl, MD, Deborah Coady, MD, Hope K. Haefner, MD, Mario Preti, MD, Jason Reutter, MD, Priya Selva-Nayagam, MD, Colleen K. Stockdale, MD, MS, and Marc Van-Beurden, MD.

Preneoplastic vulvar lesions have been recognized for almost 100 years. However, the interpretation of the pathologic and clinical characteristics of these lesions has been a matter of continuous debate. The International Society for the Study of Vulvovaginal Disease (ISSVD), since its foundation in 1970, has been among the leaders in producing terminologies of preneoplastic vulvar lesions, based on discussions among gynecologists, pathologists, dermatologists, and other members. In 2012, the ISSVD participated in the introduction of the Lower Anogenital Squamous Terminology (LAST) by the American Society for Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists.[1] This terminology is not unique to the vulva but rather aimed to unify the nomenclature of human papillomavirus (HPV)–associated squamous lesions of the entire lower anogenital tract. It recommends the terms low-grade squamous intraepithelial lesion (LSIL) and high-grade SIL (HSIL) for histopathologic diagnoses of productive HPV infections, which includes external genital warts and precancers, respectively.

However, in relation to vulvar lesions, the following concerns were raised[2]:

The first concern was that in LAST, which deals only with HPV-associated lesions, the term "differentiated vulvar intraepithelial neoplasia (differentiated VIN)"—generally a non-HPV–associated intraepithelial neoplasia—is not included. Differentiated VIN has a higher risk of progression to invasive cancer than HPV-associated precancerous conditions of the vulva.[3] Two different types of squamous VIN were introduced in the 1986 ISSVD terminology and confirmed in 2004[4]: "usual VIN" (HPV associated, with approximately 20% of the burden of invasive cancer) and "differentiated VIN" (not HPV associated, with approximately 80% of the burden of invasive cancer).[5,6] The absence of reference to differentiated VIN in the LAST consensus terminology was regarded as potentially perilous, because it could lead to its being overlooked by health care providers, despite its malignant potential. However, it was recognized that LAST was referring specifically to HPV-related conditions.

The second concern was that by including vulvar LSIL, LAST has recreated the potential for overdiagnosis and overtreatment for benign and at times self-limiting lesions. The ISSVD 2004 terminology[4] of VIN discontinued the use of VIN 1 (now "LSIL"), saying that "VIN 1 is not a precancerous lesion in the vulva but rather the reaction of the skin to HPV infection. Accordingly, vulvar LSIL, as with LSIL in any sites of the lower genital tract, should not be considered or treated as potentially neoplastic lesions." However, various participants in LAST did not accept the ISSVD position on LSIL and argued that LSIL does have a significant role in the vulva.[7]

The ISSVD assigned the terminology committee the task of developing a terminology that will take these concerns into consideration, recognizing that the LAST has been endorsed by the ISSVD.

The present article introduces the 2015 ISSVD terminology of vulvar SILs and describes the debates and deliberations that led to its formation.

TABLE 1. Historic Terminologies of Vulvar SILs

1922	Dyskeratose erythroplasiforme de la muqueuse vulvaire
1929	Bowen dermatosis
1943	Carcinoma in situ
1961	1. Intraepithelial carcinoma of Bowen
	2. Intraepithelial carcinoma simplex type
1972	Vulvar atypia
1973	Bowenoid atypia
1976	(ISSVD) Hyperplastic dystrophy with atypia
1979	Bowenoid papulosis
1982	VIN
1986	(ISSVD) VIN 1–3, VIN 3, differentiated type
1989	(WHO) VIN 1–3
1994	(WHO) SIL
2004	(ISSVD) VIN usual and VIN differentiated
2012	(LAST) LSIL and HSIL
2014	(WHO) LSIL, HSIL and VIN differentiated

ISSVD indicates International Society for the Study of Vulvovaginal Disease; VIN, vulvar intraepithelial neoplasia; WHO, World Health Organization; SIL, squamous intraepithelial lesion; LAST, Lower Anogenital Squamous Terminology; LSIL low-grade SIL; HSIL, high-grade SIL.

A Historic Perspective

The history of the terminology for vulvar SILs has been reviewed with the previous 2 concerns in mind and is summarized in Table 1. The ISSVD terminologies are presented and compared with LAST in Table 2. The first description of VIN was reported as "dyskeratose erythroplasiforme de la muqueuse,"[10,11] and was later referred to as "Bowen dermatosis."[11] In 1958, Woodruff and Hildebrandt[12] introduced the term "carcinoma in situ" of the vulva. This term became the leading name for many years. In 1961, 2 distinct types of carcinoma in situ were recognized, a simplex type and Bowenoid type.[13]

In 1976, the ISSVD terminology committee published the "new nomenclature for vulvar disease—histopathological classification of vulvar dystrophies."[8] It consisted of vulvar dystrophies, vulvar atypia (with or without dystrophy), Paget disease of the vulva, and squamous cell carcinoma in situ.

In 1982, the term "VIN" was first introduced,[14] and in 1986, the ISSVD adopted it as a general category of intraepithelial squamous neoplasia.[9] It was subdivided into squamous (may include HPV change) and nonsquamous, with the squamous type consisting of VIN 1 (showing mild atypia), VIN 2 (moderate atypia), and VIN 3 (severe atypia, carcinoma in situ), and the nonsquamous type including Paget disease and melanoma in situ.

Pertinent to the current discussion is that the ISSVD added the term "differentiated-type VIN 3" to the 1986 terminology. This was defined as "those cases that have cells with prominent eosinophilic cytoplasm, often with keratin or 'pearl-like' changes in the involved epithelium. These changes are usually seen near the tip of the rete ridges in the lower third of the epithelium. The epithelial cell nuclei in these areas usually have prominent nucleoli with vesicular, rather than coarsely clumped chromatin. The more superficial epithelium may show some maturation."[9]

Also related to the present report is that a large worldwide review of 2,000 cases of VIN and invasive vulvar carcinoma has demonstrated HPV DNA in 86.7% of VIN and 28.6% of invasive vulvar carcinoma.[15] This strongly suggests that other factors are more involved than on the cervix where HPV is present and regarded as the causative agent in virtually 100% of cervical intraepithelial and invasive neoplasia. The vulva, unlike the cervix, is composed of skin and keratinized epithelium and there is no transformation zone. Consequently, the effect of HPV infection on the vulva is not biologically equivalent to that on the cervix or anus.

In 2004, the ISSVD presented a VIN classification that applied 2 VIN groups and abandoned the grading of VIN to 1–3.[4] The 2 VIN groups were "VIN, usual type, HPV related," containing histopathological subcategories of warty, basaloid, and mixed (warty, basaloid); and "VIN, differentiated type, HPV unrelated," characterized by a high degree of cellular differentiation. One of the originalities of that terminology was that the term VIN 1 was discarded, because of the new perception that it actually represented only benign HPV infection or reactive changes.

In 2012, LAST, a uniform terminology for female and male lower genital tract and anal-perianal HPV-related SIL, was initiated.[1] The term "SIL" was a preferred term to the VIN/cervical intraepithelial neoplasia/penile intraepithelial neoplasia terminology. The SIL lesions were graded by a 2-tier system "HSIL" and LSIL, abandoning the 3-grade terminology of VIN 1, 2, or 3. The choice of the 2-tier terminology was based on its being recognized and more reproducible by pathologists than the previous one.

The LAST terminology was endorsed by the ISSVD, despite the 2 concerns that were raised, as detailed in the introduction.

Considerations in the Choice of the Terminology

In 2014, the World Health Organization published the fourth edition of its book "WHO Classification of Tumours of Female Reproductive Organs."[16] The LAST's LSILs and HSILs were used and, in addition, "VIN-differentiated type" was applied as well.

Because the ISSVD endorsed LAST, the terminology committee discussed several approaches to developing a terminology, which will keep LAST, while answering the concerns raised.

Reintroduction of differentiated VIN in addition to LAST, by staying with the term VIN, dividing it to "VIN, HPV associated"

TABLE 2. Comparison of the ISSVD Terminologies and LAST of Vulvar Squamous Intraepithelial Neoplasia

Year of publication	Friedrich[8] (1976)	Wilkinson et al.[9] (1986)	Sideri et al.[4] (2004)	Darragh et al.[1] (2012, LAST)
Terminology categories	Vulvar atypia	VIN 1	Flat condyloma or HPV effect	LSIL (VIN 1)
	A. Without dystrophy	VIN 2	VIN, usual type (Bowenoid, basaloid, mixed)	HSIL (VIN 2,3)
	B. With dystrophy			
	Squamous carcinoma in situ	VIN 3		
		Differentiated VIN	VIN, differentiated type	—

VIN indicates vulvar intraepithelial neoplasia; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

and "VIN, non-HPV associated" (differentiated type) could reduce the confusion between the 2 categories of the preneoplastic intraepithelial lesions. However, the studies that have examined HPV DNA presence sometimes failed to depict HPV in all cases of high-grade vulvar SIL, and on the other hand, some differentiated VIN cases contained HPV DNA.[17,18] Therefore, the division to HPV-associated and non-HPV–associated VIN was deemed inaccurate.

The suggestion of using LSIL as in LAST also raised objection, because vulvar LSIL, which is the equivalent of VIN 1, is a poorly reproducible diagnosis that probably carries no clinical relevance, is rarely diagnosed, and is treated only if symptomatic. The publication that was used by the LAST committee to claim that vulvar LSIL is a well-founded entity[7] has been criticized as representing only a benign HPV lesion.[19] Instead, the decision was to make it clear that LSIL meant "flat condyloma or HPV change."

The terminology committee also discussed using the 2014 WHO classification of tumors of the vulva (see Table 3),[16] as is. In this classification, SIL, which is the new name of intraepithelial neoplasia, is further divided into the following 3 categories: LSIL, HSIL, and differentiated-type VIN. Benign squamous lesions, such as condyloma acuminatum, are listed separately.

It seemed to the committee that the ISSVD could adopt the WHO classification, if it would have been made clear that LSIL is not a precancerous lesion but rather a condyloma or HPV change.

DISCUSSION

The impact of terminology for vulvar intraepithelial lesions has been significant over the years. In the past, the use of the terms vulvar carcinoma in situ and vulvar intraepithelial carcinoma led to the concept that every intraepithelial neoplastic lesion carried a high neoplastic potential and should be removed by extensive surgery with adequate margins.[20] Later, the introduction of the term VIN clarified that the low-grade lesions of the vulva may be treated expectantly. In LAST, the separation into low- and high-grade lesions further underlined the difference between the low malignant potential of LSIL that may be observed versus the high malignant potential of HSIL.[1] The LAST has been endorsed by the ISSVD, and the aim of the present terminology committee was to resolve the concerns that pertain to the application of LAST to the vulva.

TABLE 3. 2014 WHO Classification of Tumors of the Vulva[16]

Epithelial tumors
Squamous cell tumors and precursors
SILs
LSIL
HSIL
Differentiated-type VIN
Squamous cell carcinoma
Keratinizing
Nonkeratinizing
Basaloid
Warty
Verrucous
Basal cell carcinoma
Benign squamous lesions
Condyloma acuminatum
Vestibular papilloma
Seborrheic keratosis

SIL indicates squamous intraepithelial lesion; LSIL, low-grade SIL; HSIL, high-grade SIL; VIN, vulvar intraepithelial neoplasia.

TABLE 4. 2015 ISSVD Terminology of Vulvar SILs

- LSIL of the vulva (vulvar LSIL, flat condyloma, or HPV effect)
- HSIL of the vulva (vulvar HSIL, VIN usual type)
- DVIN

SIL indicates squamous intraepithelial lesion; LSIL, low-grade SIL; HPV, human papillomavirus; HSIL, high-grade SIL; VIN, vulvar intraepithelial neoplasia; DVIN, differentiated-type VIN.

After analyzing all options, the committee concluded that the 2 concerns regarding the LAST could be addressed by accepting a modified form of the WHO classification. The version that was finally adopted by the ISSVD (see Table 4) does contain LSIL. However, the word "neoplasia" is not used, replaced by "lesion," and in parentheses, it is stated that the meaning of this term is a flat condyloma or HPV effect. This expresses the approach of the ISSVD that LSIL is not precancerous and does not need to be treated, unless symptomatic.

Then, the term HSIL is used, maintaining in parentheses the previous term of usual VIN. "Vulvar intraepithelial neoplasia differentiated" is the third category, just as in the previous ISSVD terminologies.

The advantages of this terminology are that it includes all types of vulvar intraepithelial lesions, and in addition, it is close to the WHO classification as well as the LAST that is used by The American Society for Colposcopy and Cervical Pathology and College of American Pathologists creating unity among clinicians and pathologists. The 2015 ISSVD terminology provides a reasonable solution to the 2 concerns that were raised by ISSVD with regard to LAST.

This terminology was presented, discussed, and accepted by a majority vote at the ISSVD World Congress on July 28, 2015. The ISSVD executive council recommends that the present terminology replace all previous versions of terminology of VIN.

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