Cervical Screening Recommendation for non HIV-infected Immunosuppressed Women

Chair: Anna-Barbara Moscicki

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Do Non-HIV Immunocompromised Patients Require Special Treatment?

Disclosures

- No financial relationships or conflict of interest to disclose

Overall Objectives

- To summarize current knowledge of cervical cancer, SIL, and HPV infection in immunocompromised (non-HIV) women

- To provide recommendations for cervical cancer screening and initial triage of abnormal results in these women based on literature review and expert opinion.

Should we be following those recommended for HIV infected women?

- Greatest number of cross-sectional and prospective studies are available for HIV infected women (no randomized trials)
- Problem is that the health of HIV infected women are likely now more robust than those with severe iatrogenic immunosuppression
- Recommendations for screening remain vague and uncertain.

Methods

Expert panel with diverse clinical backgrounds including adolescent medicine, family medicine, infectious disease, epidemiology, surgery, oncology, and obstetrics and gynecology.

Three areas with 5-10 key words

1) Autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and diabetes mellitus (DM)
2) Solid organ transplants (SOL)
3) Post stem cell transplants (PSCT).

Methods

- All the abstracts generated by the search were reviewed by each of the groups, and if any appeared relevant, articles were then reviewed in detail.
- More recent articles (within 10 years) were considered priority for review.
- Recommendations for screening from each group were largely based on expert opinion.
- Adherence to screening, health benefits and risks and available clinical expertise
- A formal cost-benefit analysis was not possible.
- Treatment strategies were not reviewed.

Current Cervical Cancer Screening Recommendations for HIV:

HIV-Infected Women Aged <30 years

- Screening should commence within 1 year of the onset of sexual activity but no later than 21 years old.

- Cervical cytology at the time of initial diagnosis with HIV and then annual.
- If the results of the 3 consecutive tests are normal, follow up screening should be every 3 years.
- Co-testing is not recommended

Triage of Abnormal Pap Test Results

- ASC-US/ HPV + referral to colposcopy regardless of age.
- If HPV testing is not available or not done or negative, then repeat cytology in 6 to 12 months
- For any result of ASC-US + on repeat cytology, referral to colposcopy regardless of age.
- LSIL or worse (including ASC-H, AGC and HSIL) referral to colposcopy regardless of age.

HIV-Infected Women Aged ≥30 years

- Cervical cancer screening in HIV-infected women should continue throughout a woman's lifetime (and not, as in the general population, end at 65 years of age).
- Either cytology only or co-testing (cytology plus HPV) is acceptable for screening-co-testing preferred.
- Primary HPV screening has not been addressed.
- Cytology alone and ASC-US with HPV triage: intervals and refer for abnormal results the same as <30 years of age.
- Co-test negative (i.e., a normal Pap and negative HPV test) → repeat cervical cancer screening in 3 years.

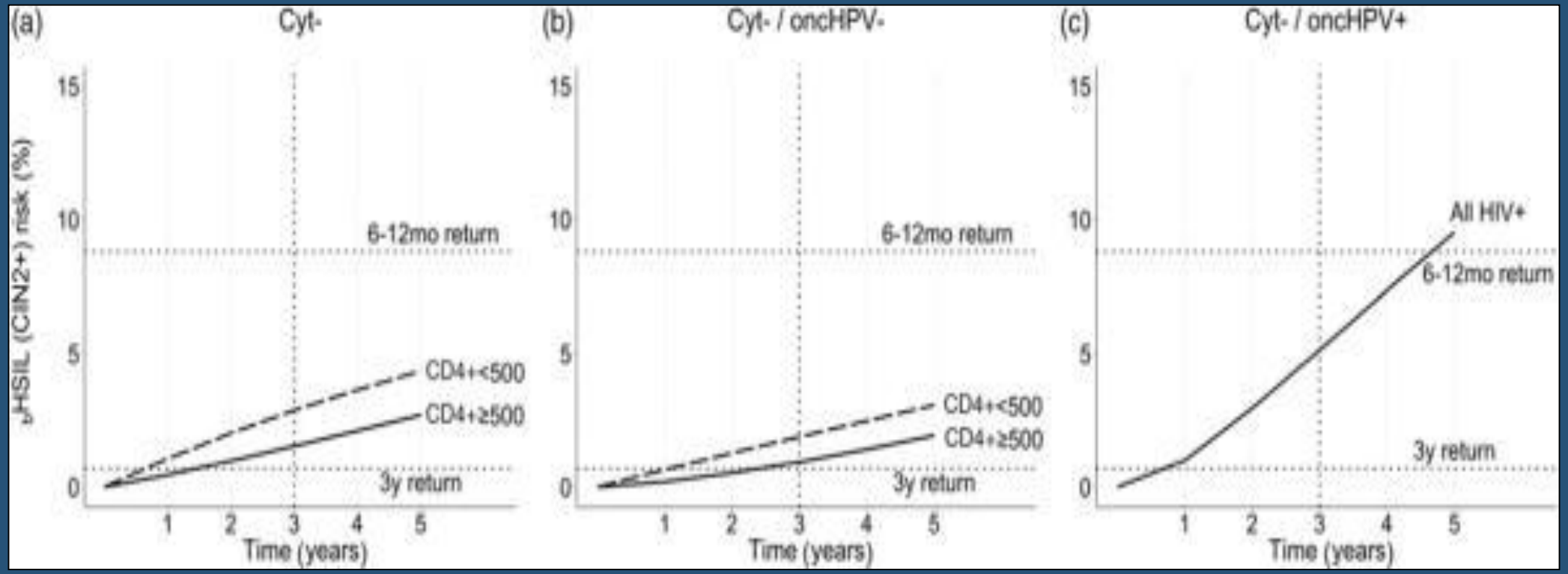
Triage of abnormal test results

- LSIL or worse regardless of HPV → refer to colposcopy
- Cytology negative/hrHPV → return in one year

Risk based strategies

- None are available in immunosuppressed women non HIV
- Robbins et al recently performed a risk based strategy analysis comparing to general population and the current CDC guidelines

Risk of cervical bHSIL+ among 2049 WLHIV following single negative cytology (Cyt-), by CD4+ cell count at the time of cytology and oncogenic HPV status, compared with general population risk benchmarks for recommending women be rescreened in 3 years (3-year return) or 6-12 months (6-12-month return)



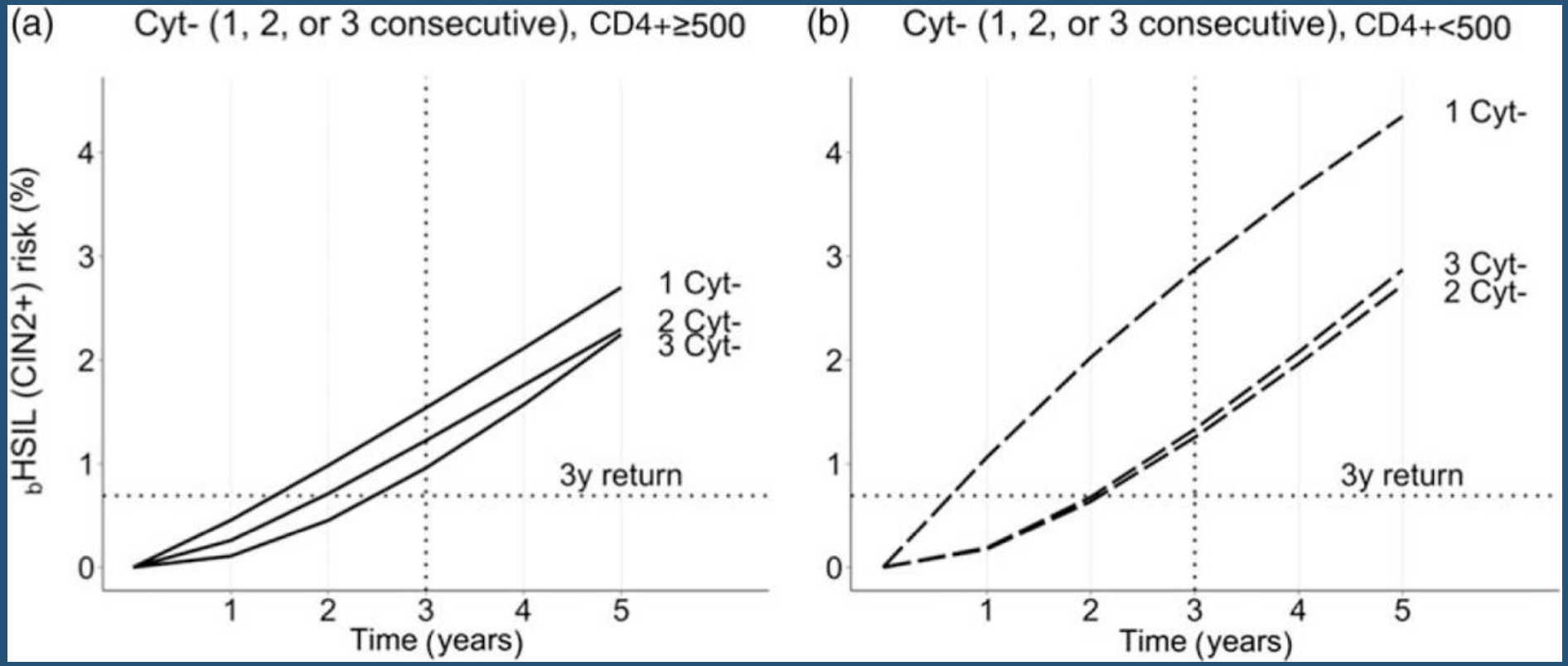
Robbins. AIDS, 2017

Summary of biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse (cervical intraepithelial neoplasia grade 2 or higher) risks among women living with HIV and the cervical cancer screening strategies suggested by this risk benchmarking approach.

			Observed$_b$ HSIL+ (CIN2+) risk, % (95% CI) at:				
Cytology	oncHPV	CD4+ cell count	1 year	2 years	3 years	Risk-based strategy	CDC guideline [14]
Negative	Negative	≥500 <500	0.20 (0–0.51) 0.66 (0.08–1.2)	0.53 (0–1.1) 1.3 (0.47–2.1)	0.94 (0.21–1.7) 1.9 (0.87–2.9)	3-year return 2-year return[a]	3-year return
	Unknown	≥500 <500	0.46 (0.10–0.81) 1.1 (0.51–1.6)	0.98 (0.44–1.5) 2.0 (1.2–2.8)	1.5 (0.83–2.3) 2.9 (1.9–3.9)	2-year return 1-year return	1-year return
	Positive	Any	1.0 (0–2.4)	3.0 (0.40–5.5)	5.1 (1.7–8.6)	1-year return	1-year return[b]

Robbins. AIDS, 2017

Risk of cervical bHSILR (CIN2R) among WLHIV following one, two, or three consecutive negative cytology results (Cyt-), by CD4R cell count at final cytology: (a) at least 500 cells/ml; (b) less than 500 cells/ml, compared with the general population risk benchmark for recommending women be rescreened in 3 years (3-year return).



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			Observed$_b$ HSIL+ (CIN2+) risk, % (95% CI) at:				
Cytology	**oncHPV**	**CD4+ cell count**	**1 year**	**2 years**	**3 years**	**Risk-based strategy**	**CDC guideline [14]**
3 negative	**Unknown**	**≥500** **<500**	**0.11 (0–0.30)** **0.19 (0–0.46)**	**0.45 (0.02-0.89)** **0.68 (0.12–1.2)**	**0.96 (0.31–1.6)** **1.3 (0.52–2.1)**	**3-year return** **2–3-year return**	**3-year return**

Robbins. AIDS, 2017

Risk of cervical [b]HSILR (CIN2R) among 374 WLHIV following ASC-US cytology, by CD4R cell count at the time of cytology and oncogenic HPV cotest status, compared with general population risk benchmarks for recommending women be rescreened in 3 years (3-year return), 6–12 months (6–12-month return), or referred for immediate colposcopy.

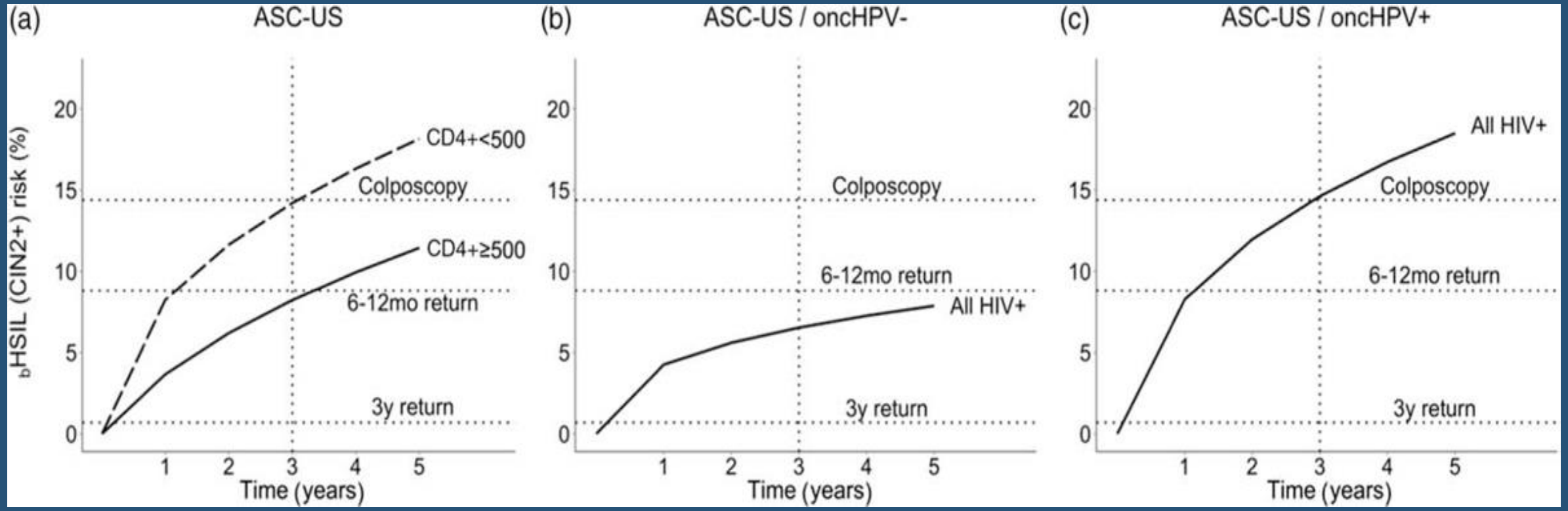

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Table 2. Summary of biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse (cervical intraepithelial neoplasia grade 2 or higher) risks among women living with HIV and the cervical cancer screening strategies suggested by this risk benchmarking approach.

			Observed[b] HSIL+ (CIN2+) risk, % (95% CI) at:				
Cytology	oncHPV	CD4+ cell count	1 year	2 years	3 years	Risk-based strategy	CDC guideline [14]
ASC-US	Negative	Any	4.3 (1.6–6.9)	5.6 (2.4–8.8)	6.5 (2.9–10.1)	6–12-month return	(Not stated)
	Unknown	≥500 350–499 <350	3.7 (0.62–6.7) 6.9 (2.4–11.4) 8.9 (5.3–12.6)	6.2 (2.2–10.2) 9.0 (3.4–14.4) 13.1 (8.6–17.7)	8.2 (3.3–13.2) 10.4 (4.3–16.5) 16.4 (11.1–21.7)	6–12-month return 6–12-month return Colposcopy	6–12-month return
	Positive	Any	8.3 (3.2–13.3)	12.0 (5.7–18.2)	14.6 (7.4–21.8)	Colposcopy	Colposcopy

Robbins. AIDS, 2017

Summary of studies on IBD and risk of SIL and Cervical Cancer (CC)

Author	Outcome	Design	Study Population	Result
Hutfless et al 2008	CC	Case-control 1996-2006	KPNC CD (427); UC (738) control (12,124)	No risk overall or by Rx
Lees et al 2009	SIL	Retrospective	CD (184) UC (178); control (1448)	No risk overall or by Rx
Kim et a 2015	HSIL/CC	Population based cohort 1979-2012	US commercial insurance database IBD (25,176)	No risk
Hemminki et al 2102	CC	Retrospective Case-control	Swedish data base CD (12,886) UC (14,272)	No risk
Singh et al 2009	SIL/CC	Population-based nested case control	Cancer registry and National data base	No risk except ↑ risk of ≥ASC-US if use of both corticosteroids and immunosuppressant (trend for HSIL)
Rungoe et al 2015	SIL/CC	Population-based 1979-2011	Danish registry CD (8717) ;UC(18, 691)	↑ risk HSIL in UC but not CC ↑ risk of HSIL & CC in CD ↑ risk with TNFa antagonist and azathioprine for HSIL but not CC in women with CD ↑ risk of CC before Dx
Jess et al 2013	SIL/CC	Population cohort	CD (441) UC (707)	↑ risk with 5-aminosalicyslic acid and thiopurine in women with CD
Allegretti et al 2015	HSIL/CC	Meta-analysis	IBD (77,116)	↑ risk HSIL/CC if on immunosuppressive Rx

Summary of studies on SIL and CC of Solid Organ Transplants

Author	Outcome	Design	Study Population	Result
Adami J et al 2003	CC	Population based database linkage	Swedish transplant registry 1970-1997 5,931 cases	No risk for CC but ↑ risk for anal, penile, vulvar Ca
Madeleine et al 2013	CIS/CC	Linkage of transplant cohort and cancer registries	US Scientific Registry of Transplant Recipients 1987-2009 187,649 cases	No risk overall for CC but ↑ risk for anal, penile, vulvar Ca except in 18-34 yo ↑↑risk of CIS and ↑ risk of CC
Kasiske et al 2004	CC	Population-based	Medicare billing for kidney SOT 1995-2001 SOT 35,765 cases	↑↑ risk (another study ↑ with time post transplant)
Silverberg et al 2018	CIN 2+	Nested case control HIV and non HIV immune suppression	Integrated health care system 1996-2014 cases with CIN 2+, SOT in 119	↑↑ risk with 1+ immunosuppressants similar to risk HIV CD4<500 ↑ risk overall
Engles et al 2011	CC	Linkage of transplant cohort and cancer registries	US Scientific Registry of Transplant Recipients 1987-2008 SOT 175,732 cases	No risk for CC but ↑ for anal, penile, vulvar Ca
Vajdic et al 2006	CC	Population-based record linkage	Australia and New Zealand Dialysis and Transplant Registry SOT 4,214 cases	↑ CC during dialysis and post-transplant

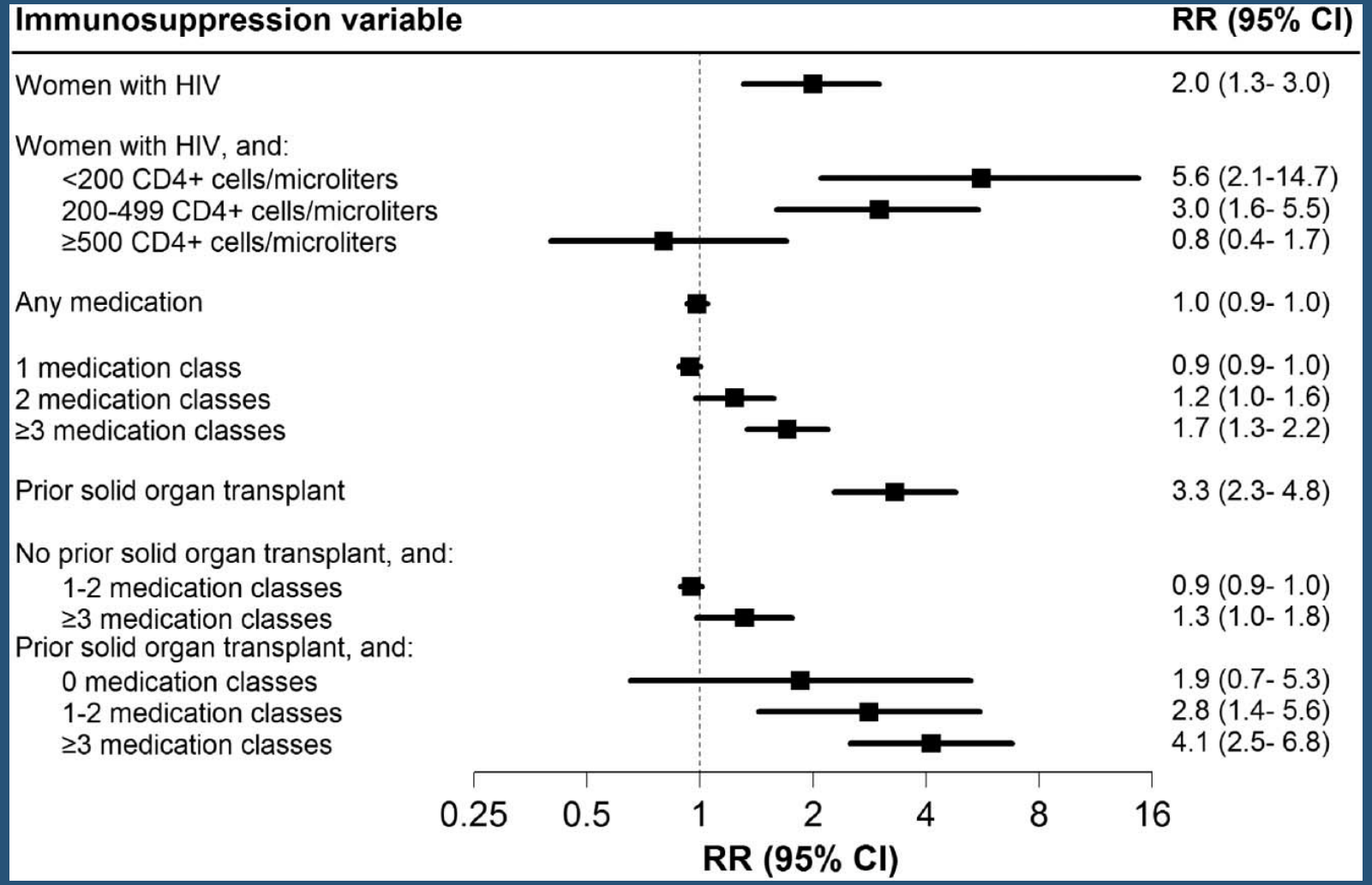
Summary of studies of CC and SIL in women with SLE and RA

Author	Outcome	Design	Study Population	Results
Santana et al 2011	CC/ SIL	Systematic Review	33 articles in SLE pts (all small n's)	15 studies showed ↑ SIL 3 studies showed ↑ HSIL ↑ risk with ↑ immunosuppression 14 studies No risk of CC
Dey et al 2013	CC	Nested case control	595 pts with SLE	↑↑ risk
Simon et al 2015	CC	Meta-analysis	13 articles in RA Pts	Overall no risk 3 articles ↓ show ; 1 article ↑ risk
Tam et al 2004	ASCUS+	Case-control	85 pts with SLE and 2000 control	↑↑ SIL; no change in risk with Rx
Dugue et al 2014	HSIL	Meta Analysis	14,000 pts with SLE	↑ risk with cumulative dose effect of Azathioprine (also mentioned no risk for CC)
Askling et al	CC	Population based Registry linked	6,366 Pts with RA	No risk; no change in risk with anti-TNFa exposure
Setoguchi et al	CC	Population based using health care utilization records	1,152 pts with RA exposed to anti-TNFa compared to MTX	↓ risk for CC with anti-TNFa compared to MTX

Summary of studies of HSCT

Author	Outcome	Design	Study Population	Results
Chang, 2018	CC/SIL	Systematic review	4 studies on SIL, 13 studies on CC; most pts with allogeneic HSCT	↑risk SIL with chronic GvHD or vulvovaginal GvHD; no increased risk CC in large studies, ↑ risk in studies with N<1000
Shanis, 2018	Any HPV, SIL, multifocal HPV, persistence	Retrospective and prospective longitudinal	82 allogeneic HSCT pts	↑risk HPV and SIL with extensive GvHD or vulvovaginal GvHD; pre-transplant HPV associated with post-transplant HPV
Wang, 2012	SIL, HPV	Retrospective case series	96 allogeneic HSCT pts	↑risk SIL with vulvovaginal GvHD and unrelated HLA donor
Majhail, 2011	CC	Retrospective cohort	4318 (1903 female) allogeneic HSCT pts	No increased risk invasive CC
Rizzo, 2009	CC	Retrospective registry	28,874 (11,752 female) allogeneic HSCT pts	No increased risk invasive CC
Bhatia, 2001	CC	Retrospective cohort	2129 (919 female), 64% allogeneic HSCT pts	↑ risk of invasive CC
Sasadeusz, 2001	Cytology	Retrospective chart review	64 BMT pts	↑ risk of SIL
Curtis, 1997	CC	Retrospective registry	19,229 (7851 female), 97% allogeneic HSCT pts	No increased risk invasive CC

Immunosuppression and adjusted rate ratios (RRs) for CIN 2+



Silverberg MJ et al. Obstet Gynecol. 2018 Jan

Definition for High Risk Screening:

IBD:

- women on chronic (> 3months) corticosteroids or immunomodulators (methotrexate, azathioprine, or mercaptopurine).

SLE and RA

- Women on 2 or more chronic immunosuppressants

Solid Organ Transplants

- All patients on any immunomodulatory

Post Stem Cell Transplant

Women with history of abnormal CC screening or gGVHD

Post Stem Cell Transplant and Diabetes Mellitus

- No increased risk overall noted
- But adherence may be questionable and there should be due diligence to maintain routine screening

Screening for high risk immunosuppressed women (non-HIV) <30 years

Similar to CDC recommendation for HIV

- Start within 1 year of immunosuppression
- Screening should start within 1 year of sexual debut
- Cytology ONLY recommended
- Return in 1 year for 3 consecutive cytologies

Similar to HIV <500 (Robbins et al)

- If previous documented 3 normal cytologies may go to screening interval every 2 years

Screening for high risk immunosuppressed women (non-HIV) ≥30 years

Similar to CDC recommendation for HIV

- Start within 1 year of immunosuppression
- Screening should start within 1 year of sexual debut

Cytology only

- If using cytology return in 1 year for 3 consecutive cytology

Similar to HIV <500 (Robbins et al)

- If previous documented 3 normal cytologies may go to screening every 2 years

Screening for high risk immunosuppressed women (non-HIV) ≥ 30 years

Similar to CDC Recommendation for HIV

- Start within 1 year of immunosuppression
- Screening should start within 1 year of sexual debut

Co-testing:

Similar to CDC Recommendation for HIV

- cytology-/hrHPV+ : 1 year return
- cytology-/HPV 16/18: referral to colposcopy

Similar to HIV <500:

- Cytology-/hrHPV-: 2 year return

Robbins. AIDS, 2017

Management of abnormal cytology

Similar to CDC Recommendation for HIV

- **ASCUS/HPV+**
- **LSIL/ HSIL regardless of age and HPV status**
  - ➢ **immediate referral to colposcopy**

- **ASCUS (HPV unknown or HPV negative)**
  - ➢ **return in 6-12 months**
  - ➢ **if severely immunocompromised consider colposcopy**

Robbins. AIDS, 2017

Thank You