**PICO Question 9:** For women who are at higher risk of cervical cancer due to immunosuppression what is the safety and effectiveness of screening using strategies other than those recommended for the general population compared to those recommended for the general population

| Population | Study design | Intervention | Control | Outcome |
|---|---|---|---|---|
| Chronically immuno-suppressed or immuno-compromised asymptomatic women*<br><br>**Potentially immuno-suppressed or immuno-compromised women<br><br>Organ transplant recipient women<br>Or<br>HIV-positive women | Screening randomized or pseudo-randomized controlled trial | Modified recommended screening strategy:<br>starting at an age <25 years<br>and/or<br>screening intervals less than 5 years<br>and/or<br>referring all HPV positive women to colposcopy irrespective of reflex cytology result | Recommended screening strategy<br>Primary HPV screening every 5 years from ages 25 – 69 years using partial genotyping with women positive for HPV16/18 referred to colposcopy and women positive for other oncogenic types undergoing cytology triage | Cervical cancer mortality<br>Cervical cancer diagnosis<br>Precancerous high grade lesion detection |

**SUMMARY OF GUIDELINES**

| Guideline, developer and references | Evidence based SR | Relevant recommendations |
|---|---|---|
| Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. **Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America**<br>Online with regular updates; last update Dec 17 2015 | Unclear | Recommended to continue throughout a woman's lifetime (not end at 65 as per general population)<br>**Women aged <30:**<br>• Pap within 1 year of commencement of sexual activity and no later than age 21. For women diagnosed at 21-29 years, Pap at time of diagnosis, then every 12 months (BII). If three consecutive Paps are negative, next Pap should be in three years. (BII) Co-testing is not recommended.<br>• Colposcopy referral for ASC-US with positive reflex HPV test or LSIL+. Repeat Pap at 6-12 months in women who are ASC-US and either HPV negative or HPV not done. Colposcopy for ASC-US+ at repeat.<br><br>**Women aged 30 or older:**<br>• Pap at time of diagnosis, then every 12 months (BII). If three consecutive Paps are negative, next Pap should be in three years.<br>• Colposcopy referral for ASC-US with positive reflex HPV test or LSIL+. Repeat Pap at 6-12 months in women who are ASC-US and either HPV negative or HPV not done. Colposcopy for ASC-US+ at repeat<br>or<br>• Co-test at time of diagnosis or at age 30. Co-test negative women can be re-screened in three years.<br>• Colposcopy referral for HPV16/18+ or ASC-US with positive HPV test or LSIL+. Repeat co-test at 6-12 months in women who are cytology negative and positive for non-16/18 HPV or positive for an unknown hrHPV type. Repeat co-test at 6-12 months in women who are ASC-US and either HPV negative or HPV not done. At repeat co-test, colposcopy for any test positive (ASC-US+ or any hrHPV positive). |
| **Screening for cervical cancer.**<br><br>**American College of Obstetricians and Gynecologists (ACOG). Screening for cervical cancer. Washington (DC); 2012 Nov. 17 p. (ACOG practice bulletin; no. 131). [111 references]** | Unclear appears to be based on other guidelines | **The following recommendations are based on good and consistent scientific evidence (Level A)**:<br>Women who have a history of cervical cancer, have human immunodeficiency virus (HIV) infection, are immunocompromised, or were exposed to diethylstilbestrol in utero should not follow routine screening guidelines. |

| Guideline, developer and references | Evidence based SR | Relevant recommendations |
|---|---|---|
| **Gynecologic care for women with human immunodeficiency virus.**<br>American College of Obstetricians and Gynecologists (ACOG). Gynecologic care for women with human immunodeficiency virus. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2010 Dec. 18 p. (ACOG practice bulletin; no. 117). | No consensus | **The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B)**:<br>• Human papillomavirus testing currently has no role in the triage of HIV-infected women with abnormal cytology results or for follow-up after treatment for cervical intraepithelial neoplasia (CIN).<br>• Women with HIV infection should have cervical cytology screening twice in the first year after diagnosis of HIV and annually thereafter.<br>• Routine colposcopy is recommended for HIV-infected women with atypical squamous cells of undetermined significance (ASC-US) or higher grade abnormality. |
| Society of Obstetricians and Gynaecologists of Canada<br>**Colposcopic management of abnormal cytology and histology 2012**<br>Bentley et al., (2012) Colposcopic management of abnormal Cervical Cytology and histology J Obstet Gynaecol Can 34 (12) 1188-1202 | Yes (could not find documentation) unless otherwise stated when evidence is insufficient | Immunocompromised women do not require screening colposcopy. (II-2D) |
| European AIDS Clinical Society Guidelines version 8.0 October 2015 | | **HIV positive women**<br>Cervical cytology every 1-3 years for sexually active women. "HPV testing may aid screening". |
| **European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, Part 2 2009**<br>**Jordan et al., (2009) Cytopathology 20:5-16** | | **HIV positive women**<br>Annual cytology should be performed with an initial colposcopy if resources permit. |
| **Cervical cancer screening clinical practice guideline.**<br>Kaiser Permanente Care Management Institute. Cervical cancer screening clinical practice guideline. Oakland (CA): Kaiser Permanente Care Management Institute; 2010 Oct. 152 p. [96 references] | ? unsure cannot access | **Screening in Women at Increased Risk of Cervical Cancer**<br>**6.A.** For immunosuppressed or human immunodeficiency virus (HIV)-positive women, cytology and HPV testing are recommended at six months following treatment for CIN2/3, and again at 24 months, with colposcopy for any positive result. Routine screening every three years can then be resumed indefinitely. **Consensus-based**<br>**6.B.** For immunosuppressed or HIV-positive women, if HPV testing is not done, two cytology tests at six and 12 months after treatment for CIN2/3 are |

| Guideline, developer and references | Evidence based SR | Relevant recommendations |
|---|---|---|
| | | recommended, with colposcopy for any positive result, then annual cytologic screening indefinitely. **Consensus-based**<br>**6.C.** At least annual cytology with or without HPV testing is recommended for women who are immunosuppressed or HIV-positive. **Consensus-based** |
| **Cancer screening.**<br>**University of Michigan Health System**. Cancer screening. Ann Arbor (MI): 2012 Oct. 18 p. [21 references]<br>Based on :<br>Saslow et al 2012 ACS/ ASCCP/ ASCP guidelines<br>ACOG 2009 guidelines<br>NCCN 2012 guidelines<br>NCI guidelines 2010<br>USPSTF guidelines 2012 | No | More frequent screening, usually annual cytology, with or without HPV testing, is recommended for women who are immunosuppressed, infected with human immunodeficiency virus (HIV), or were exposed to diethylstilbestrol (DES) in utero *[IC]*.<br>For other high-risk women, screening continues until limited life expectancy no longer warrants *[1D]*. |
| **Colposcopy and Programme Management Guidelines for the NHS Cervical Screening Programme Second edition** 2010<br><br>**NHS** | ?<br>Based on evidence otherwise consensus | The risks and benefits of cervical screening for HIV positive women receiving antiretroviral treatment and for chronically immunosuppressed women have yet to be fully evaluated. (See section 11.)<br>Women taking maintenance immunosuppression medication post transplantation who have no history of CIN should have cervical screening in accordance with national guidelines for the non-immunosuppressed. Any abnormal cervical cytology result should prompt colposcopic referral. Women with a previous history of CIN should have routine follow up as recommended for the immunocompetent population.<br>Women receiving long term cytotoxic drugs for rheumatological disorders should have regular cytological screening in accordance with national guidelines.<br>There is no indication for increased surveillance in the following situations<br>• women receiving cytotoxic chemotherapy for non-genital cancers<br>• women receiving long term steroids<br>• women receiving oestrogen antagonists such as tamoxifen.<br>All women newly diagnosed with HIV should have cervical surveillance performed by, or in conjunction with, the medical team managing the HIV infection. Annual cytology should be performed with an initial colposcopy if resources permit. |
| **Spanish Guidelines for cervical cancer prevention 2014**<br>**Eurogin abstract only** | consensus | Immunocompromised women: 1. Cytology annually from age 21; 2. Co-testing from age 30 (every 3 years if CD4 > 200cl/uL or Active antiretroviral therapy but annually if CD4 <200cl/uL or no antiretroviral treatment) |

**LITERATURE REVIEW**

***SUMMARY OF FINDINGS***

- Prevalence of infection with oncogenic HPV types (hrHPV) is generally higher in immunosuppressed women. Immunosuppression is hypothesised to increase prevalence via inhibiting the immune system's capacity to keep latent infections in check (reactivation) and/ or to clear newly acquired infections. Studies examining HIV+ women in particular are often confounded by increased risk behaviour in HIV+ compared to HIV- women.
- Studies have varied in their findings as to whether there is an increase in cervical cancer in immunosuppressed women. Studies examining women with regular screening have found no significant difference; while studies with no screening or infrequent screening have found higher cancer incidence in immunosuppressed women. Authors have hypothesised that the reason for the differences is the extent to which immunosuppressed women have been screened, and that the effect of immunosuppression is secondary to that of [effective] screening. Some studies have reported lower participation in screening in immunocompromised women, especially transplant recipients [Meeuwis et al, 2015; Meeuwis et al, 2012; Wang et al, 2012]. The influence of screening on risk is indirectly supported by findings from several studies that risk in immunosuppressed people is much more greatly elevated for non-cervical HPV-related cancers (anal, vaginal, vulval; for which effective screening is not available) than for cervical cancer, even though the HPV attributable fraction for these cancers is lower than for cervical cancer.
- Studies which have undertaken genotyping have found HPV16 to be the most common type in both HIV+ and HIV- women.
- One study examined clearance by HPV type group (16 vs non-16/18 oncogenic HPV) and found clearance of HPV16 was similar in HIV+ and HIV- women, but HIV+ women were less likely than HIV- women to clear non-16/18 HPV types.
- Two studies were useful in examining the potential use of HPV-based screening in HIV+ women:
    - One US study found that among women who were cytology negative and hrHPV negative at baseline, the five-year cumulative risk of CIN2+ and of CIN3+ was similar in HIV+ and HIV- women (5%, 95% CI:1-8% versus 5%, 95% CI:2-8% respectively in HIV+ versus HIV- women for CIN2+; 0.5%, 95% CI: 0-2% versus 0.7%, 95% CI: 0-2% respectively for CIN3+). However the number of cases was small in this study.
    - The same study also examined outcomes in women who were cytology negative but hrHPV positive at baseline (same caveat applies re small number of cases). Cumulative risk for CIN3+ among women who were HIV+ and positive for HPV16 was 10% (95% CI:0-23%) at three years, and no additional cases were detected by five years (no women were positive for HPV18). Cumulative risk for CIN3+ among women who were HIV+ and positive for non-16/18 HPV types was 3% (95% CI: 0-6%) over five years. Cumulative risk among HIV- women was not stratified by HPV16/18 vs non-16/18 hrHPV types. Five-year cumulative risk for CIN2+ who were cytology negative, but positive for any hrHPV type was 10% (95% CI: 0-21%) for HIV- women versus 16% (95% CI: 9-23%) for HIV+ women overall; 14% (95% CI: 2-25%) for HIV+ with CD4 count ≥500; 12% (95% CI: 0-22%) CD4 count 350-499; and 22% (95% CI: 9-34%) CD4 count <350. Authors concluded that 12 month follow-up could be considered for HIV+ women who were cytology negative and non16/18 hrHPV positive, but that colposcopy referral was recommended for HIV+ women who were cytology negative andHPV16 positive.
    - A study among previously unscreened women in South Africa found that the sensitivity of HPV testing (Hybrid Capture 2; HC2) for CIN2+ and CIN3+ was at least as high in HIV+ women as it was in HIV- women, and that negative predictive value was similar in HIV and HIV- women. In this group, specificity was lower in HIV+ women than in HIV- women. Among those who were HC2 positive, the type distribution was similar in

HIV+ and HIV- women. Combined prevalence of HPV16/18 (as a percent of infections) was almost identical in HIV+ vs HIV- women in all age groups when stratified by histologically-confirmed disease status.

- Some studies have recommended that cervical screening be done prior to transplantation in order to ensure there is no undetected disease, as this is otherwise at risk of progressing and is harder to treat post-transplantation.

***TRANSPLANT RECIPIENTS***

**Table 1 - Review articles: transplant recipients**

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| Nguyen<br>2013<br>USA | Review | Immunosuppressed transplant recipients (study also examined other sources of immunosuppression) | Most data is from renal transplant recipients (RTR).<br>Some (but not all) studies have reported higher prevalence of hrHPV in RTR cf the general population.<br>Large cohort studies in Sweden and the USA found no difference in the rates of cervical cancer in organ transplant recipients cf immunocompetent counterparts; authors hypothesised the effect of being an organ transplant recipient was secondary to that of effective screening.<br>Authors of review state studies are needed to look at HPV testing and partial genotyping in immunocompromised women, and that at present, prudent approach is yearly cytology after transplantation (or from age 21 in young recipients of transplants). |
| Dugué<br>2013<br>Denmark | Systematic review | Immunosuppressed transplant recipients (study also examined other sources of immunosuppression) | Most studies found an increased risk of ICC in organ transplant recipients (included studies reported on renal, heart, liver or any transplantation) cf general population. One recent US cohort study (N=68,705 women with organ transplants in 1987-2008; N=45 ICC cases) found no increased risk among organ transplant recipients, and interpreted it as a benefit of screening. |
| Chin-Hong<br>2013<br>USA | Review | Immunosuppressed transplant recipients | Scottish study from late 1980s found higher prevalence of CIN and HPV16/18 in RTR cf age-matched controls.<br>South Korean study of 453 women who received a renal transplant 1990-2008 found a cervical cancer incidence of 58.1/100,000 patient-years, 3.5-fold higher than in general population.<br>Review has a focus on making recommendations (US-based |

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| | | | and justification not always clear). Screening recommendations appear to be based on 2009 recommendations (as above, Kaplan *et al*, MMWR Recomm. Rep. 2009) for HIV+ women and their general recommendation that same interval be used in organ transplant recipients as in HIV+ women. |
| Shanis<br>2012<br>USA | Review | Females who have undergone allogeneic haematopoietic stem cell transplantation (allo-HSCT) | One study reported long-term allo-HSCT survivors had 13-fold increased risk of cervical cancer cf general population and 18.5-fold higher if the all-HSCT survivor is older than 34 years. Authors report that in their institution 20% had high grade cervical dysplasia (cytology?) (follow-up time frame not stated). Abnormal cytology (any grade) was detected a median of 51months post-HSCT and was associated with IST for cGVHD. Recommendation focus. For screening this was annual cytology with reflex HC2 for cyto negative or ASC-US. Referral threshold unclear but either ASC-H (Table 1) or either of ASC-US with positive HC2 triage test or persistent ASC-US (text) |
| Grulich<br>2007<br>Australia | Systematic review and met-analysis of cohort studies | Immunosuppressed transplant recipients (study also examined other sources of immunosuppression) | Organ transplant: 97% renal transplant<br><br>Meta-analysis SIR (95%CI)<br>• Cervical cancer (3 studies, 22 cancers): 2.13 (1.37 – 3.30)<br>Comparison with SIRs from other HPV-related cancer sites (not restricted to females):<br>• Vulva and vagina (2 studies, 33 cancers): 22.76 (15.8 – 32.7)<br>• Anus (2 studies, 18 cancers): 4.85 (1.36-17.3)<br>• Penis (1 study, 6 cancers):15.79 (5.79-34.4)<br>• Oral cavity & pharynx (3 studies, 49 cancers): 3.23 (2.40-4.35) |

SIR: standardised incidence ratio; CI confidence interval; ICC: invasive cervical cancer; hrHPV: high risk (ie oncogenic) HPV; IQR: interquartile range; RTR: renal transplant recipient. IST: ; cGVHD: chronic graft-versus-host disease

**Table 2 – Primary studies published in 2012 or later (not covered by review articles): transplant recipients**

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| Meeuwis<br>2015<br>The Netherlands | Cohort (mainly baseline cross-sectional data presented) | 218 renal transplant recipients aged 18 or older, who received transplant 1968-2008; with functioning donor kidney Feb 2012.<br>Mean age at baseline 55.4 years (SD 12.2) | HPV DNA testing done on samples which were self-collected using dry Evalyn brush; $SPF_{10}$ $LiPA_{25}$<br>Prevalence of hrHPV: 17.4% (95% CI: 12.9-23.1)<br>Prevalence of any HPV type was higher in this group (27.1%) than in general Western European female population aged 45-55 (9-10%)<br>Time on and type of immunosuppressive therapy were not associated with positivity for HPV (any type)<br>HPV positive women were offered screening. Of 38 who were hrHPV+ who attended for screening, 6 were HSIL on cytology; 8 were moderate or severe cervical dysplasia over follow-up period of at least 12 months (mean 20 months).<br>Relatively high proportion of study participants had no sexual contact in previous 6 months (49%) and had not had more intensive cervical screening as recommended (only 22% at least one smear per year; 12% no screening in past 5 years) |
| Marschalek<br>2015<br>Austria | Retrospective observational cohort | 262 female kidney graft recipients who received transplant 1980-2012, were attending for routine post-transplantation follow- up visits in one of two hospitals in Vienna, and aged 18 or older at time of clinic attendance. | Based on clinical data from hospital records, electronic patient records, and in some cases records from the woman's gynaecologist/ GP, 6 patients developed CIN2/3, and 15 developed any CIN (median follow-up 101.1 months; IQR: 27.3-190.7 months).<br>Proportional incidence rate for any CIN (not available separately for CIN2 or CIN3):<br>1-year: 1.3%<br>3-year: 2.7%<br>5-year: 4.2%<br>10-year: 12.0%<br>In multivariate analysis, incidence of female genital dysplasia (including VIN and VaIN) was associated with multiple transplantations and younger age at transplantation. |
| Aggarwal<br>2014<br>India | Cross-sectional | 40 women who received a renal transplant at least 6 months earlier (median age: 40; range 24-69) (RTR)<br>80 controls attending | Conventional cytology performed with residual cells from cytobrush used for HPV testing using PCR Hybribio HPV genotyping array kit (Hong Kong).<br>No cytological abnormalities in any woman (inflammation in 3/40 (7.5%) RTR & 17/80 (21%) controls).<br>Prevalence of hrHPV was 1.9 times higher in RTR cf controls |

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| | | gynaecology outpatient unit (median age: 38; range 27-72) who "*had a normal cervix on examination*".<br>Women "*previously diagnosed with preneoplastic or neoplastic lesions of the cervix were excluded*" (unclear if histologcal only or also includes cytological abnormalities)<br>Time period not stated.<br>Patients from a single institution. | (P=0.18):<br>RTR: 13/40 (32.5%)<br>Controls: 14/80 (17.5%)<br>HPV16 most common type in both RTR (5/40; 12.5%) and controls (10/80; 12.5%) and the prevalence was the same in both groups. Next most common types in RTR were HPV31 (5/40; 12.5%) and HPV18 (4/40; 10%), each of which was detected in 2/80 controls (2.5%).<br>No correlation between HPV positivity (any of 21 types including oncogenic and non-oncogenic) and duration of immunosuppression in RTR.<br>Authors acknowledge lack of power to detect differences between RTR and controls.<br>Potential bias due to requirement that controls have "*a normal cervix on examination*" (further details not provided). |
| Skov Dalgaard<br>Denmark<br>2013 | Observational cohort using data from national administrative databases | Patients treated with renal replacement therapy (dialysis or transplantation) for at least 90 days as recorded on Danish Nephrology Registry. Matched population controls from the national Civil Registration System. | Modest increase in ICC risk (crude incidence rate ratio (IRR) =1.81; 95% CI 1.01-3.23), compared to much greater increases in anal (IRR=4.54) and vulvovaginal (IRR=5.81) cancers. Risk was similar in both transplant and dialysis patients. Authors suggest that cervical cancer risk in this study would reflect longstanding availability of systematic cervical screening program in Denmark. |
| Madeleine<br>USA<br>2013 | Observational cohort using linked data from a national transplant registry and 15 state/ local cancer registries. | Transplant recipients (TR) who received their transplant when aged 18 or older and resident in a region covered by a cancer registry at the time of transplant. | Cervical cancer risk was no higher in TR than expected based on general population rates (SIR=1.0).<br>Some cancer registries collected data on *in situ* cervical cancer (CIS). Based on a subset of female transplant recipients living in areas where cancer registries recorded CIS (N=17,010), risk of *in situ* cervical cancer was elevated compared to expected rates (SIR=3.3; 95% CI: 2.6-4.2)<br>Authors suggest lack of difference in cervical cancer is likely due to effective screening, and state that "The Kidney Disease: Improving Global Outcomes group suggested that screening for cervical cancer in transplant recipients should follow the general population guidelines". |

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| Meeuwis<br>2012<br>The Netherlands | Retrospective observational cohort | 1023 female patients who underwent RT in one hospital in Nijmegen, the Netherlands between 1968-2008, and with renal transplant function of at least 90 days. Censored at 31 July 2010. | Five RTR were diagnosed with cervical cancer.<br>Median time between transplant and cervical cancer diagnosis: 5.0 years (range 2.2-9.8).<br>Median age at cervical cancer diagnosis: 59.3 years (range: 37.2-69.7)<br>hrHPV types detected in 5 cervical cancer specimens: HPV16 (3), HPV18 (1), HPV56 (1).<br>3/5 had no record of cervical screening prior to RT; 1 of whom also had no record of screening post-RT.<br>1/5 had CIN3 diagnosed pre-RT (approx. 5 years pre-RT); first cytology post-RT (@41 months) was HSIL; policy was wait-and-see only – no histology available; cancer diagnosed @9.8 years post-RT<br>1/5 had LSIL cytology 31 months but no subsequent histology prior to RT; first cytology post-RT (@26 months) was HSIL and subsequent histology was cervical cancer.<br>In all 5 cases, the possibility could not be ruled out that precancer existed prior to RT (and in one case it was known to have done so).<br>Only 1/5 cases had cytology within 12 months of transplant. In this case, cytology was LSIL and cervical cancer was diagnosed approximately 7 years later. |
| Wang<br>2012<br>Norway | Retrospective cohort | 89 patients who underwent allogenic stem cell transplantation (allo-SCT) between 1985-2005 in one hospital which was the sole transplantation centre in Norway, and who survived for at least 5 years post-transplant (all but 1 still alive at Nov 2010). Median age at transplant: 39 years. Follow-up until most recent cervical smear before August 2010. Median follow-up [from | Leukemia was the indication for allo-SCT in 92.1% patients.<br>Median duration of immunosuppressive therapy 12 months (range:0-78 months)<br>Only 11/89 attended for all recommended cytology tests in the first 5 years following transplantation (9 visits recommended; mean number of cytology tests for all 89 patients 6.5; range 2-9)<br>Among 69 patients with normal cytology prior to transplantation, the incidence of cytological HSIL after transplantation was 23.2% (16/69) over the follow-up period.<br>Post-transplantation HPV status (based on HC2; in-house PCR typing of HC2 positives) was available for 43/89 patients; 27.9% were hrHPV positive. Methods state that HC2 was used in women with ASC-US (TBS 2001 classification) or LSIL cytology, however there may have been other circumstances where it was also used as HPV status is available for 5 women with negative cytology (1/5 hrHPV positive) |

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| | | transplant]: 11 years; range 5-25. | |
| Pietrzak<br>2012<br>Poland<br><br>and<br><br>Mazanowska<br>2013<br>Poland | Cohort | 60 kidney graft recipients (RTR) plus 60 healthy controls under routine gynaecological care at the same hospital in Warsaw, recruited 2007-2008. Restricted to ages 28-48 and those with negative Pap smear in previous 12 months. | RTR were less likely than controls to have had ≥ 2 lifetime sexual partners (16/60 cf 33/60)<br>Baseline test results:<br>RTR: 11/60 (18%) hrHPV+; 2/11 abnormal cytology (2 x HSIL); 2/2 CIN2+<br>Controls: 15/60 (25%) hrHPV+; 2/15 abnormal cytology (LSIL, HSIL); 2/2 CIN2+<br><br>At 24 months, most hrHPV infections detected at baseline had cleared in RTR (81.8%; 9/11) and controls (93%; 14/15).<br>Among those who were still hrHPV+ at 24 months:<br>RTR: 2/2 had negative cytology; 2/2 E6/E7 mRNA+; 1xCIN3, 1xneg histology<br>Controls: 1/1 HSIL cyto; 1/1 E6/E7 mRNA+; 1 x CIN3<br>NB: follow-up cyto/ colp/ histo at 24 months only done for those who were E6/E7 mRNA+<br><br>Authors acknowledge that the study's finding that hrHPV prevalence is similar (or possibly lower) in RTR than in controls could be due to: i) the age of participants (studies which have included younger women have found younger women more likely to have hrHPV infection than older women), and ii) the differences in the number of sexual partners between RTR and controls within this study. |

SIR: standardised incidence ratio; CI confidence interval; ICC: invasive cervical cancer; IRR: incidence rate ratio; hrHPV: high risk (ie oncogenic) HPV; IQR: interquartile range; RT: renal transplantation; RTR: renal transplant recipient

***HIV***

**Table 3 - Review articles: HIV**

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| Cobucci<br>2015<br>Brazil | Systematic review & meta-analysis | Individuals with HIV/ AIDS | Meta-analysis of cancer incidence in the post- vs pre-HAART eras. Individual included studies would have defined what was considered pre- vs post-HAART.<br>Five studies compared cervical cancer incidence in the pre- vs post-HARRT era. The point estimates from all five included studies indicated an increase in cervical cancer incidence in the post-HAART era compared to the pre-HAART era. The overall rate ratio of incidence in post- vs pre-HAART eras was 1.46 (95%CI: 1.09-1.94; P=0.04; $P_{heterogeneity}$=0.56). |
| Denslow<br>2014<br>USA | Systematic review (search end date: 31 January 2012) | HIV-positive women | Based on 3 studies in developed settings, incidence of cytology HGSIL estimated as:<br>HIV+ women: 0.7-6.2 per 100 woman-years<br>HIV- women: 0.3-1.4 per 100 woman-years<br>Appears to be an increasing risk of incidence of *any* cytological SIL with decreasing CD4 count in HIV+ women, but only significant in one study for women not on ART (but adjusted for HPV detection). One study showed reduced incidence of any cytology SIL among HIV+ HAART users cf HIV+ non-users, however most studies showed no significant difference by HAART use.<br>Results were not available for incidence of HG lesions or cytology by CD4 count or ART use.<br><br>Progression of abnormalities<br>Estimated progression rate from ASCUS/ LSIL/ CIN 1 to >LSIL in HIV+ ranged from 1.2-26.2 per 100 woman-years. Only 3 studies had HIV- comparator: progression rates were ~twice as high in HIV+ cf HIV- women. ART use was mixed in all 3 studies i.e. in all studies, HIV+ women were not all on ART. In the only study which looked at both HIV+ and HIV- women in terms of at least partly histologically-defined outcomes, 8/202 HIV+ women progressed from CIN1 to CIN2-3/HSIL over a mean follow-up period of 40 months (i.e. 1.2 cases per 100 woman-years). There were no cases identified in 21 HIV- women who were also followed up. |

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| | | | Two studies on progression from LSIL to HSIL (cyto confirmed by histo) stratified by CD4 count. Cumulative risk of progression appeared to be higher in women with lower CD4 count however statistical significance was only reported for one study. No included studies reported progression stratified by ART use, however two studies published after the cut-off for the analysis found lower risk of progression or increased likelihood of lesion regression is consistent users of HAART.<br><br>Study authors note limitations due to:<br>• Likely confounding in incidence data by shared behavioural risk factors for HIV and HPV<br>• Small sample size in strata probably contributed to lack of statistical significance in differences by CD4 counts<br>• ART use differs over time and between study populations e.g. number of drugs used and whether ART use initiated in only patients with lowest CD4 count vs all HIV+ |
| Nguyen<br>2013<br>USA | Review | HIV-positive women (study also examined other sources of immunosuppression) | HIV+ women have higher prevalence of other (non-16/18) high risk HPV types cf HIV- women, and multiple-type infections are more common. Lower prevalence of HPV16 and higher prevalence of HPV 18/33/51/52/58 in HIV+ women with HSIL cf general population of women with HSIL.<br>Two cohort studies found higher CD4 count and increased time on cART were associated with lower ICC risk within HIV+ women.<br>Two USA cohorts reported different findings for ICC risk in HIV+ women. One study found no difference in ICC risk between a cohort of HIV+ women enrolled in a care program where they received 6-monthly cervical screening and that from SEER data. A second cohort found SIR of 4.1 for HIV+ women compared to SEER data, however use of screening in this group was unclear: 6/17 ICC cases no had screening in previous 5 years.<br>Women with 3 consecutive negative Pap tests may be eligible for screening at a longer interval than 1 year.<br>One USA cohort found that women with negative cytology and negative HPV DNA on endocervical lavage at baseline had the same risk of HSIL over 3-5 year follow-up period regardless of whether they were HIV+ or HIV-. Risk of CIN2+ or HSIL did not differ by |

| Study | Study Design | Population | Comments/Results |
|---|---|---|---|
| | | | immune status, but risk for *any* SIL was higher in HIV+ women and increased with decreasing CD4 count. |
| Dugué<br>2013<br>Denmark | Systematic review | HIV-positive women (study also examined other sources of immunosuppression) | Updated data since Grulich 2007 confirms cervical cancer SIR 5.8<br>Association between CD4 count & risk of cervical cancer unclear.<br>At population level, HAART does not appear to have reduced cervical cancer in people with HIV/AIDS; however some evidence that incident cervical abnormalities more likely to clear in women on HAART and regression was positively correlated with CD4 count.<br>Among 312 HIV-infected women free of cervical lesions at baseline followed for 7 years, regression of SIL was observed in 12.5% (95% CI: 9.9-15.1%) of women on HAART but no women not on HAART.<br>In a separate cohort study, women adherent to HAART were more likely to clear oncogenic HPV infections than non-adherent women (OR: 3.7; 95% CI: 1.4-9.9) |
| Grulich<br>2007<br>Australia | Systematic review and meta-analysis of cohort studies | HIV-positive women (study also examined other sources of immunosuppression) | Meta-analysis SIR (95%CI):<br>• Cervical cancer (6 studies, 104 cancers): 5.82 (2.98 – 11.3)<br>Comparison with SIRs from other HPV-related cancer sites (not restricted to females):<br>• Vulva and vagina (2 studies, 21 cancers): 6.45 (4.07 – 10.2)<br>• Anus (6 studies, 303 cancers): 28.75 (21.6 - 38.3)<br>• Penis (3 studies, 21 cancers): 4.42 (2.77 - 7.07)<br>• Oral cavity & pharynx (4 studies, 238 cancers): 2.32 (2.40 – 4.35) |

SIR: standardised incidence ratio; CI confidence interval; ART antiretroviral therapy; HAART highly active antiretroviral therapy; cART combined antiretroviral therapy; ICC: invasive cervical cancer; CD4 count: number of CD4 T lymphocytes per $mm^3$ (cells/ $mm^3$);

**Table 4 – Primary studies published in 2012 or later (after reviews): HIV**

| Study | Study Design | Population | Comments/Results |
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| Keller<br>2015<br>USA | Cohort | HIV+ and HIV- women enrolled in 1994-1995 and 2001-2002; in both groups restricted to women with negative or LSIL cytology at baseline. Women with LSIL | HPV DNA testing performed on cervicovaginal lavage samples<br>16% of HIV+ women reported that they were on HAART; 67% had CD4 count >350 cells/µL.<br>Although HIV+ women reported fewer recent sexual partners cf HIV- women, they had a higher prevalence of hrHPV (15% vs 5%; |

| Study | Study Design | Population | Comments/Results |
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| | | cytology were included as a benchmark risk group for the colposcopy referral threshold | P<0.0001)<br>5-year cumulative risk of CIN3+:<br>HIV- women with negative cytology: no cases<br>HIV+ women with negative cytology and HPV test: ≤1% in each CD4 strata<br>HIV+ women with negative cytology & HPV16+: 10% (95% CI: 0-23%) [no women HPV18+]<br>HIV+ women with negative cytology & positive for non-16/18 hrHPV types: 3% (95% CI: 0-6%)<br>HIV- women with LSIL cytology [study threshold for colp referral]: 7% (95%CI: 3-11%)<br>In multivariate analyses, women who were HPV16+ with negative cytology were at >13 times higher risk of CIN3+ over 5 years cf women who were hrHPV-. This increased hazard ratio was non-significantly higher than that for women with LSIL at baseline.<br>Results were similar when restricting to HIV+ women, controlling for HIV RNA level and HAART use. Year of enrolment was not associated with CIN3+ risk.<br>Authors conclude that colposcopy referral is appropriate for women with negative cytology who are HPV16+ and that 1-year follow-up may be appropriate for women who are positive for other (non-16/18) hrHPV types |
| Keller<br>2012<br>USA | | HIV+ and HIV- women enrolled in 1994-1995 and 2001-2002; in both groups restricted to women with negative cytology at baseline. Most results are reported on women who are additionally hrHPV negative. Women have semi-annual visits where cytology and cervicovaginal lavage samples are collected; colposcopy is recommended when cytology is ASC-US or greater (according to TBS2001) | No hrHPV detected in cervicovaginal lavage sample:<br>HIV+: 88% (95% CI: 84-91%)<br>HIV-: 95% (95% CI: 88-94%)<br>Five-year cumulative incidence of CIN3+ (2 cases CIN3; one each in HIV+ and HIV-):<br>HIV+:0.5% (95% CI: 0-2%)<br>HIV-: 0.7% (95% CI: 0-2%)<br>Five-year cumulative incidence of CIN2+ (15 cases):<br>HIV-: 5% (95% CI: 1-8%)<br>HIV+ CD4 ≥500: 6% (95% CI: 2-10%)<br>HIV+ CD4 350-499: 2% (95% CI: 0-7%)<br>HIV+ CD4 <350: 2% (95% CI: 0-7%)<br>Difference in cumulative incidence between HIV- and HIV+ estimated as:<br>CIN2+ : 0%; (95% CI: -4 to 5%)<br>HSIL+ : -0.1%; (95% CI: -0.9 to 0.9%) |

| Study | Study Design | Population | Comments/Results |
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| | | | Five-year cumulative incidence of *any cytological SIL* differed by host immune status, but cumulative incidence of CIN2+, HSIL+ and any CIN did not.<br>Follow-up was available beyond 5 years but authors note continued incremental loss to follow-up. One additional case of CIN3 was observed between 8 and 9 years of follow-up in an HIV+ women CD4≥500 (none beyond year 5 in HIV- women). No cases of cancer were observed in all 9 years of observation. |
| McDonald<br>2014<br>South Africa | Cohort (comprising 3 cohorts recruited into 3 sequential screening studies) | 1371 HIV+ (median age 34 years; IQR 26-38) and 8050 HIV- women (median age 38 years; IQR 33-45) with no prior screening who were recruited into 1of 3 screening studies in Capetown. HIV testing was undertaken as part of study. | HIV+ women were younger, less educated, less likely to be employed, less likely to be married, more likely to be treated for an STI, more likely to use condoms and had a younger age at first intercourse cf HIV- women.<br>Colposcopy undertaken in ~86% of women, including all women in 2 cohorts and ~half of those from the third (women testing positive on one or more of HPV testing (HC2), VIA, cytology (ASCUS referral threshold) or cervicography). In the cohorts where all women underwent colposcopy, no woman who was both HPV negative and cytology negative was found to have cervical disease (not futher defined), therefore the authors considered verification bias was likely to be minimal.<br>HPV testing was performed using HC2 with genotyping of test positives via a prototype PCR array using PGMY09/11 primers provided by Roche, or (if no genotype was detected using the prototype array) using Linear Array.<br>The prevalence of hrHPV, CIN1, CIN2 and CIN3 were higher in all age groups in HIV+ than in HIV- women. For hrHPV prevalence, the difference was smaller in women aged 17-19 years (75.0% in HIV+ vs 60.2% in HIV-; P=0.06), but in other age groups prevalence of infections in HIV+ women was approximately double than in HIV-. In contrast to infections, the difference by HIV status was greatest in younger women (<35) for CIN2 and CIN3.<br>When restricted to women who tested HC2 positive, the proportion of women with CIN3 did not differ significantly by HIV status, however the proportion with CIN2 was higher in HIV+ women (i.e. PPV of HC2 for CIN2+ is higher in HIV+ than in HIV- women, but PPV for CIN3 did not differ significantly by HIV status).<br>Sensitivity of HC2 was generally higher in HIV+ women than in HIV- women (although it was high in both groups; 96.4% vs 90.9% |

| Study | Study Design | Population | Comments/Results |
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| | | | respectively for CIN3; 100% vs 81.8% respectively for CIN2; 99.2% vs 85.5% for CIN2+). Negative predictive value was similar for both HIV+ and HIV- women (99.8% vs 99.5% respectively for <CIN2).<br>Only minor differences were observed in distribution of HPV types in HIV+ vs HIV- women when stratified by biopsy-confirmed disease status. Combined prevalence of HPV16/18 was almost identical HIV+ vs HIV- women in all age groups when stratified by histologically-confirmed disease status.<br>Authors conclude that primary screening with hrHPV testing is appropriate in HIV+ women.<br>Limitations: no detailed clinical information re severity of HIV eg CD4 count, viral load, ART use. Likely women with severe HIV disease are under-represented. Likely confounding in some results for prevalence due to differences in behavioural risk factors for HIV+ vs HIV- women. |
| Blitz<br>2013<br>Canada | Cohort | HIV+ and HIV- women aged 15-44 followed over 1993-2002.<br>Semi-annual visits included cytology (TBS 1991) and HPV testing on cervicovaginal lavage and/or tampon samples.<br>Inclusion criteria for HIV- women included >3 lifetime sex partners.<br>333 HIV+ and 134 HIV- women were included in analysis of HPV acquisition/ clearance; 326 HIV+ and 130 HIV- women were included in SIL analysis | Women with abnormal cytology (apparently as LSIL threshold, but unclear) were referred for colposcopy +/- biopsy as indicated.<br>HPV testing using MY09/MY11/HNB01 primers and PGMY-line blot assay (including high and low risk types); 99.8% concordance with these genotyping assays. This analysis appears to have only used HPV test results from cervicovaginal lavage samples.<br>HPV acquisition and clearance was assessed using observed data and a 2-state Markov model. Progression and regression from SIL were estimated using observed data and a (separate) 3-state Markov transition model (No SIL, SIL, treatment for SIL/ICC, where SIL state included ASC-US, LSIL, HSIL and ICC). A sensitivity analysis grouped ASC-US with No SIL, but findings from this sensitivity analysis were reported not to differ from the main findings.<br>HPV16 most prevalent type in both HIV+ and HIV- and did not differ by HIV status. Prevalence of HPV 31,33,39,45,52,56,58 significantly higher in HIV+ cf HIV- women. Among HIV+ women hrHPV prevalence 39% among those using HAART at enrolment vs 48% in those not (P=0.09).<br>In a univariate, 2-state model, acquisition of hrHPV was higher in HIV+ women and younger women. Acquisition of HPV16 was higher in those with CD4 count <200 than those where it was higher, but did not differ by HIV status overall. Clearance of HPV16 was not associated with HIV status, but clearance of non 16/18 HPV types |

| Study | Study Design | Population | Comments/Results |
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| | | | was lower in HIV+ than HIV- women. Clearance of non-16/18 types (but not HPV16) was also associated with HAART use.<br>In univariate, 3-state model, SIL acquisition was higher in women with hrHPV and >5 lifetime sexual partners. SIL clearance was higher in those using HAART and >5 lifetime sexual partners. Progression from SIL present to treated was higher in those with HPV16.<br>Limitations: Median follow-up time was ~10 months longer for HIV+ women cf HIV- women. No histological endpoints and cytological SIL was a relatively broad and heterogeneous group. Data sample size limited multi-state models to univariate cf multivariate analyses. |

SIR: standardised incidence ratio; CI confidence interval; ART antiretroviral therapy; HAART highly active antiretroviral therapy; hrHPV: high risk/oncogenic HPV; cART combined antiretroviral therapy; ICC: invasive cervical cancer; CD4 count: number of CD4 T lymphocytes per $mm^3$ (cells/ $mm^3$); HC2: Hybrid Capture 2; TBS: The Bethesda System