Section 12: Screening for immune deficient participants

This section provides guidance for immune deficient participants. Much of the evidence on immune deficiency and HPV related cervical cancer and precursors has focused on participants with HIV and solid organ transplant recipients, however the evidence base for participants with other types of immune deficiencies is increasing.

The prevalence of HPV infections in HIV-positive participants is higher than the general population.[2] Meta-analysis of HIV infected participants with HPV and HSIL were more likely to have an HPV 16 or 18 infection than participants without HIV. [1] HIV infection has been consistently associated with HPV infection and pre-cancerous cervical lesions [3-5]

Early studies note that antiretroviral therapy did not reduce the incidence of cervical cancer. [6-8] Studies date from the period where antiretroviral therapy (ART) was only given to patients with low CD4 counts rather than the current treatment which is given as soon as HIV is diagnosed. A recent systematic review and meta-analysis has reported early initiation of ART and sustained adherence is likely to reduce the incidence and progression of squamous intraepithelial lesions, however further studies are required. [9]

Participants who have **received a solid organ transplant** such as a kidney, heart/lung or liver, have an increased risk of HPV associated cancers as well as an increased risk of precursor lesions of the anus, vulva, vagina and cervix. Evidence suggests the increased risk of invasive cervical cancer likely begins shortly after transplant and continues throughout the years after transplant, although there is a lack of evidence looking at the length of immunosuppression and/or time post-transplant and its impact on the risk of cervical cancer. [10] Furthermore, the incidence of HPV-associated cancers in women with conditions leading to solid organ transplant such as end stage renal disease, may be higher than in women of the general population. [11] Therefore ongoing surveillance is recommended [10,12-15]

A systematic review from 2018 by Chang et al [16] reported mixed evidence for increased risk of cervical cancer following Haemopoietic Stem Cell Transplantation (HSCT). There was no overall increased risk of invasive cervical cancer in women after HSCT, however this study also noted that some smaller studies showed a

statistically significant increased risk[17-19]. These conflicting results may reflect the fact that many patients did not survive long enough to evaluate the risk of slow-growing cancers, as well as there being differences in study follow-up times.

There is a growing body of evidence which reports people who take long term immunosuppressive therapy may have an increased risk of high grade cervical abnormalities and cervical cancer. [20-26] A study from China found that CIN prevalence was significantly higher in IBD patients than controls ($P < 0.001$). The HPV-infection rate was higher in patients administered methotrexate, or more than two immunosuppressant drugs. [23] For **participants taking immunosuppressive therapy** it is important to discuss the importance of cervical screening. International studies have reported poor awareness and participation in screening among immune deficient populations, highlighting the importance of education. [27 28]

Cell mediated immunity is critical to HPV control, in which macrophages serve as one of the primary cellular defenses against the pathogen. Cell mediated immunity is also activated in infection with the virus SARS-CoV-2. For this reason, and due to the paucity of evidence for the cervical cancer risk and optimal screening interval for immune-compromised/deficient groups, the draft Australian National Cervical Screening Program Guidelines have used expert opinion and the conditions included by the Australian Technical Advisory Group on Immunisation (ATAGI) for a third primary dose of COVID-19 vaccine in individuals who are severely immunocompromised, to make recommendations around cervical screening in those who are immunosuppressed but are not HIV positive and have not had a solid organ transplant. The following recommendations for screening in New Zealand are based on this Australian guidance.

Table 1 provides guidance on which immune deficient groups have or are likely to have a substantially increased risk of cervical pre-cancer and cancer, and therefore the recommended regular interval screening interval for HPV primary screening is 3-yearly rather than 5-yearly testing. This should be considered on a case-by-case basis to support clinical judgement. The specialist responsible for managing the immunosuppressant medication/s or condition may be of assistance in supporting decision-making regarding management.

Table 1: Conditions and medications where 3-yearly screening is recommended for HPV primary screening

Screening Periodicity	Conditions and Medications
3-yearly screening recommended [a]	Living with human immunodeficiency virus (HIV) Solid organ transplant with immunosuppressive therapy Active haematological malignancy Haematopoietic stem cell transplant (HSCT) recipients or chimeric antigen receptor T-cell (CAR-T) therapy within 2 years of transplantation. Primary immunodeficiency including combined immunodeficiency syndromes (e.g. systemic lupus erythematosus) major antibody deficiency (e.g. common variable immune deficiency [CVID] or agammaglobulinemia), defects of innate immunity (including phagocytic cells), defects of immune regulation, complement deficiencies and phenocopies of primary immunodeficiencies.
3-yearly screening should be highly considered [b]	Long term haemodialysis or peritoneal dialysis (>6 months) When participants are taking multiple immunosuppressant's where the cumulative effect is considered to be severely immunosuppressive Participants taking long-term treatment (>6 months) with highly immunosuppressive therapies, **Including:** High-dose corticosteroid treatment equivalent to >20 mg/day of prednisone for ≥14 days in a month, or pulse corticosteroid therapy. Selected conventional and targeted synthetic disease-modifying anti-rheumatic drugs (sDMARDS), taken for long-term treatment (> 6 months) (e.g.: leflunomide) Mycophenolate, methotrexate (≥10 mg/week), azathioprine (≥1mg/kg day), 6-mercaptopurine (≥0.5 mg/kg/day), dimethyl fumarate, etanercept, fingolimod, natalizumab, teriflunomide, tocilizumab, secukinumab. Alkylating agents (e.g.: cyclophosphamide, chlorambucil), Systemic calcineurin inhibitors (e.g.: cyclosporin, tacrolimus), JAK inhibitors (e.g.: tofacitinib, baricitinib, ruxolitinib, upadacitinib)

Screening Periodicity	Conditions and Medications
	Excluding: Hydroxychloroquine or sulfasalazine when used as monotherapy or low-dose corticosteroid Biologic therapies that deplete T cells (e.g.: muromonab, teplizumab) Other biologics that have other targets, for example anti-CD20 (e.g. rituximab) or anti-TNF (e.g. infliximab, adalimumab)

[a] Based on documented significantly higher risk of cervical precancer and cancer, predominantly from studies looking at risk for cervical cancer in participants with conditions listed, and some evidence extrapolated from COVID-19 mRNA vaccine response in those with primary immunodeficiency.
[b] Based on an increased risk expected through pathological mechanisms and trends from observational studies of COVID-19 mRNA response, with limited evidence from observational studies looking at cervical cancer specifically. Note: Most standard chemotherapy regimens for solid tumors are not considered to be highly immunosuppressive, as well as other antineoplastic treatments, such as hormone therapy, immunotherapy and targeted therapy. People with history of cancer and those being treated with chemotherapy short-term (< 6 months) for solid tumors, should not be considered immune-deficient in this context. Particular cases, especially with prolonged treatments or multiple prior lines of cytotoxic therapy, may be discussed with the oncologist.

There are some conditions that are **not considered immune deficient** in the context of cervical screening and participants with these conditions should not be screened in the immune deficient pathway. These include:

- Diabetes
- Thyroid disease (Graves' disease)
- Previous splenectomy
- Coeliac disease

To indicate if a participant is immune deficient and requires more frequent screening or earlier referral to colposcopy following an HPV detected (any type) test the screen taker or colposcopist can indicate if the participant is immune deficient on the laboratory request form or by contacting the NCSP.

RECOMMENDATION – SCREENING INTERVAL FOR IMMUNE-DEFICIENT PARTICIPANTS	
R13.01 Ensuring immune deficient participants have their immune status noted on the NCSP	**Practice point** Clinicians should indicate if a participant is immune deficient on the laboratory request form or by contacting the NCSP.
R13.02 Immune deficient participants with a test result of HPV not detected	**Consensus-based recommendation** Participants who are immune deficient with an HPV not detected test result should have their next HPV screening test in 3 years. This recommendation is in accordance with the World Health Organization guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.
R13.03 Immune deficient participants with a co-test result of HPV not detected and ASC-US or LSIL cytology	**Consensus-based recommendation** Participants who are immune deficient with a co-test result of HPV not detected and ASC-US or LSIL cytology should have their next HPV screening test in 3 years.
R13.04 Immune deficient participants with an HPV detected (any type) test result	**Consensus-based recommendation** Immune deficient participants who have an HPV detected (any type) test result should be referred to colposcopy.
R13.05 Colposcopy assessment and treatment in immune deficient participants	**Consensus-based recommendation** A colposcopist should assess and treat immune deficient participants with screen-detected abnormalities.
R13.06 Colposcopy of whole lower genital tract in immune deficient participants	**Practice point** The entire lower anogenital tract should be assessed, because for immune deficient participants, the same risk factors apply for cervical, vaginal, vulval, perianal and anal disease.
R13.07 Histological abnormalities of the cervix in immune deficient participants	**Practice point** Participants with histologically confirmed abnormalities should be managed according to the same guidelines as participants who are not immune deficient.
R13.08 Treatment of HSIL (CIN 2/3) lesions	**Practice point** If treatment for a cervical precancerous lesion is required for an immune-deficient participant, an excisional method should be used.

RECOMMENDATION – SCREENING INTERVAL FOR IMMUNE-DEFICIENT PARTICIPANTS	
R13.09 Test of Cure for treated immune deficient participants	**Practice point** Immune deficient participants who are treated for HSIL (CIN2/3) should complete a Test of Cure HPV test after treatment as recommended in these guidelines. Following two consecutive HPV not detected results the participant can return to three-yearly screening with an HPV test.
R13.10 Follow-up following hysterectomy for immune deficient participants	**Consensus based recommendation** Immune deficient participants with a previous high grade cervical abnormality should complete a Test of Cure HPV test. Following two consecutive HPV not detected results the participant can return to three-yearly screening with an HPV test. **A new recommendation** Immune deficient participants with no evidence of a previous high grade abnormality who have a total hysterectomy for benign reasons with no cervical pathology in the hysterectomy specimen, should continue with three yearly screening with an HPV test.
R13.11 Exiting the screening programme	**Consensus based recommendation** Immune deficient participants can exit the screening programme at aged 70 if they have an HPV not detected test result if on regular interval three-yearly screening (refer to section two for transition from the cytology-based screening programme).

SPECIAL RECOMMENDATIONS FOR IMMUNE-DEFICIENT PARTICIPANTS	
R13.12 Screening before solid organ transplantation	**Practice point** Participants aged between 25 and 74 years should have a review of their cervical screening history when they are added to the organ transplant waiting list and while they remain on the waiting list. The purpose of this review is to confirm they are up to date with recommended screening for the general population. Participants who are overdue for screening, or become due while on the waiting list, should be screened with an HPV test so that any abnormalities can be investigated or treated as necessary before transplantation and the start of immunosuppressive therapy.
R13.13 Screening participants with a new diagnosis of HIV	**Practice point** Participants aged between 25 and 74 years who have a new diagnosis of HIV should have a review of their cervical screening history to ensure they are up to date with screening in line with the recommended three-yearly interval for this group.

SPECIAL RECOMMENDATIONS FOR IMMUNE-DEFICIENT PARTICIPANTS	
R13.14 Regular screening for immune-deficient participants	**Practice point** Participants who are immune deficient should be educated about the increased risk from HPV infection and encouraged to attend for regular screening. Ask all participants/ whānau whether they require assistance or support to attend cervical screening. Consider transport, cultural support and where appropriate offer referral to support to screening services.
R13.15 Young participants with long-term immune deficiency	**Practice point** For young participants who are sexually active, and who have been immune deficient for more than five years, a single HPV test between 20 and 24 years of age could be considered on an individual basis (regardless of HPV vaccination status).
R13.16 Guidance for immune deficient participants and their screen takers	**Practice point** The specialist responsible for managing the immunosuppressant medications or condition may be of assistance in supporting decision-making regarding management.

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