Feidhmeannacht na Seirbhíse Sláinte
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Sláinte Ghnéis &
Clár um Thoirchis Ghéarchéime
Sexual Health &
Crisis Pregnancy Programme

Guidance Document on HPV Vaccination in Public HIV and STI Clinics

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1. Introduction and Background

1.1 Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) worldwide. Over 150 types of HPV have been identified and 15 HPV types are now known to be oncogenic. HPV types 6 and 11 are not oncogenic, but cause over 90% of anogenital warts in men and women. HPV is responsible for more than 90% of anal cancers, almost 70% of vaginal and vulvar cancers, more than 60% of penile cancers and over 70% of oropharyngeal cancers. Two high risk HPV types (16 and 18) cause over 70% of cervical cancers.

Men who have sex with men (MSM) and in particular HIV-infected MSM have a higher incidence of sexually transmitted infections, including HPV, compared to the general population. Following exposure, people living with HIV (PLHIV) are more likely to experience persistent HPV infection and HPV associated disease due to related immune dysfunction. HPV associated malignancies are more prevalent in MSM and PLHIV compared to the general population.

For further information on HPV and HPV associated diseases, please see **Appendix 1**. Evidence to support the extension of HPV vaccination to PLHIV and MSM in Ireland.

1.2 Background

In Ireland, the national HPV immunisation programme for girls was introduced in 2010. The HPV vaccine is currently administered through the HSE HPV school vaccination programme and is recommended for all girls in 1st year of second level school. Vaccinating the majority of girls in Ireland means that their male partners get some protection too. However boys who grow up to become MSM will get far less of this protection.

The vaccine offered in Ireland prevents against the HPV types that cause genital warts and many of the cancer causing types.

One of the priority actions in Ireland's first national sexual health strategy is to:

"Give policy consideration to extend HPV vaccine to adolescent boys and potential at-risk groups (e.g. MSM)."

Responsibility for policy decision making around extension of HPV vaccine to adolescent boys rests with the Department of Health and is subject to a full Health Technology Assessment by the Health Information and Quality Authority (HIQA). The national HPV vaccine programme may be extended to adolescent boys in the future.

The National Immunisation Advisory Committee (NIAC) has made recommendations in relation to HPV vaccination of PLHIV and MSM[1] [2]. Up to October 2016 HPV vaccine was not available free of charge to MSM and PLHIV within public HIV and STI clinics.

In 2016, the HSE Sexual Health and Crisis Pregnancy Programme (SHCPP) in collaboration with Dr. Brenda Corcoran, (Public Health Specialist, National Immunisation Office (NIO), Dr. Kevin Kelleher (Assistant National Director, Public Health) and Dr. Corinna Sadlier (Specialist in Infectious Diseases) developed a report[3] on the anticipated numbers of PLHIV and MSM eligible and likely to avail of HPV vaccine through existing public HIV and STI services from 2017 through to 2019. HIV and STI services were consulted in drafting the report. NIO initially agreed to provide HPV vaccine to these at risk groups in 2017 and the vaccine was made available to PLHIV (up to and including 26 years) attending public HIV services in October 2016 and to MSM (up to and including 26 years) attending public STI services in January 2017. NIO continued to provide the HPV vaccine in 2018 to public HIV and STI services.

In July 2018, the National Immunisation Advisory Committee (NIAC) updated the HPV vaccine recommendation. HPV vaccination is currently recommended for men and women living with HIV up to and including 26 years of age and for all MSM (including MSM living with HIV) up to and including 45 years of age[4]. NIO have agreed to provide the HPV vaccine for 2019.

2. Safety and efficacy of HPV vaccine

2.1 People living with HIV (PLHIV)

In studies of quadrivalent HPV vaccine (4vHPV), vaccination has been shown to be safe and immunogenic in HIV-positive children and adults within the age ranges assessed. Overall seroconversion rates are high in all groups, and both seroconversion rates and antibody titres are higher than with natural infection, and highest in those receiving antiretroviral therapy (ART) and showing high CD4 cell counts and a suppressed viral load.

The results of one study suggest that if the HPV vaccine proved efficacious in the HIV-positive population against vaccine sub-types, the potential reduction in anal cancer rates could be up to 61%.

[1] NIAC Guidelines Chapter 3 Immunisation of Immunocompromised Persons, updated August 2015, accessed 09/02/2017
[2] NIAC Guidelines Chapter 10 Human Papillomavirus, updated September 2016, accessed 09/02/2017
[3] Proposal for the extension of HPV Vaccination to high risk groups. HSE SHCPP, August 2016
[4] NIAC Guidelines Chapter 3 Immunisation of Immunocompromised Persons, updated 19th July 2018, accessed 02/10/2018

For detail and references, please see **Appendix 1**. Evidence to support the extension of HPV vaccination to PLHIV and MSM in Ireland.

2.2 Men who have sex with men (MSM)

In MSM, 4vHPV vaccine has been shown to prevent new HPV infection and reduce the incidence of both genital warts and anal intraepithelial neoplasia (AIN).

For detail and references, please see **Appendix 1**. Evidence to support the extension of HPV vaccination to PLHIV and MSM in Ireland.

3. Recommendations regarding the use of the quadrivalent[5] HPV vaccine (Gardasil®) as of October 2018

3.1 Who is eligible for the vaccine?

3.1.1 PLHIV

A full course of vaccination should be offered to every man and woman living with HIV up to and including 26 years attending the clinic regardless of risk, sexual behaviour or disease status who has not previously completed a full course of HPV vaccination.

3.1.2 MSM

A full course of vaccination should be offered to every MSM up to and including 45 years attending the clinic regardless of risk, sexual behaviour or disease status who has not previously completed a full course of HPV vaccination.

Any eligible individual that starts the vaccination schedule should complete the course.

3.2 How to administer the vaccine

Gardasil® is administered by intramuscular injection into the upper arm (deltoid region). One dose has a volume of 0.5ml and the vaccine is provided in a pre-filled syringe.

3.3 Documentation

Provision of vaccine should be documented in line with local policy on vaccine administration and documentation and include batch number and expiry date.

3.4 Vaccine dosing and schedule

For all individuals aged 15 years and older, three doses of vaccine, administered at 0, 2 and 6 months, are recommended.

[5] This may change to HPV9 when available

- First dose of 0.5ml of Gardasil® HPV vaccine.
- Second dose of 0.5ml two months after the first dose.
- Third dose of 0.5ml four months after the second dose.
- All three doses should ideally be given within one year, however a 24 month period is clinically acceptable.

Every effort should be made to comply with the recommended intervals between doses. However in exceptional circumstances minimum intervals may be used:

  - The minimum interval between dose 1 and dose 2 is 4 weeks
  - The minimum interval between dose 2 and dose 3 is 12 weeks

If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, ideally allowing the appropriate interval between the remaining doses[6].

People living with HIV should be given the vaccine in accordance with the routine three dose schedule above, regardless of CD4 count.

3.5 Contraindications to the vaccine

Anaphylaxis to any of the vaccine constituents.

Note:

1. Those who have had a non-anaphylactic hypersensitivity reaction to HPV vaccine may be given a subsequent dose of that vaccine if indicated.
2. Yeast allergy is not a contraindication to the HPV4 vaccine. Even though the vaccine is grown in yeast cells, the final product does not contain any yeast.

3.6 Precautions

Acute severe febrile illness; defer until recovery.

Syncope has been reported among adolescents who received HPV or other vaccines, particularly in relation to administration of first dose. Recipients should be seated during vaccine administration.

Pregnancy

HPV vaccine is not recommended during pregnancy, although there is no known risk associated with using recombinant viral vaccines during pregnancy. If a woman becomes pregnant during the vaccination series, remaining doses should be delayed until after completion of the pregnancy.

[6] NIAC Guidelines Chapter 2 General Immunisation Procedures, updated September 2016, accessed 07/04/2017

3.7 Concomitant administration with other vaccines

Gardasil® can be given at the same visit as any other recommended vaccines.

3.8 Vaccine storage

All vaccines are sensitive to heat, cold and light and must be kept at temperatures between +2 to +8^{o}C. Vaccines must be stored within this specific temperature range to ensure their potency and to comply with their licence. Gardasil® should not be frozen. Each service must ensure appropriate vaccine storage.

The 'Cold Chain' is the system of transporting, storing and maintaining vaccines within appropriate temperatures and protection from light from the time of manufacture to administration.

Effectiveness cannot be guaranteed for vaccines unless they have been stored correctly, as per national recommendations. Healthcare professionals should familiarise themselves with the HSE guidelines on vaccine ordering and storage: http://www.hse.ie/eng/health/immunisation/hcpinfo/vaccineordering/.

3.9 Vaccine supply

Clinics are responsible for managing their own stock locally.

Gardasil® (Sanofi Pasteur MSD) can be sourced through the HSE National Cold Chain Service. Further information about the HSE National Cold Chain Service and how to order vaccine supply is available here: http://www.hse.ie/eng/health/immunisation/hcpinfo/vaccineordering/.

3.10 Adverse reactions (ADRs)

The most common adverse reactions (ADRs) observed are:
Local: Localised pain, swelling and erythema are very common at the injection site.
General: Fever (≥ 38°), myalgia, fatigue and headache have been commonly reported. Syncope can occur.

For a detailed list of ADRs associated with Gardasil® please refer to the manufacturer's Summary of Product Characteristics (SPC) http://www.medicines.ie/medicine/11524/SPC/GARDASIL/ or the product insert that comes with each vaccine.

3.11 Reporting of adverse reactions (ADRs)

All suspected adverse reactions should be reported to the Health Products Regulatory Authority (HPRA) using the Yellow Card System or electronically: https://www.hpra.ie/homepage/about-us/report-an-issue/human-adverse-reaction-form. Reports should be as detailed as possible and include the batch number of the vaccine.

4. HPV vaccine data collection

4.1 HPV key performance indicators (KPIs)

The following indicators will be compiled at a national level by the HSE Sexual Health & Crisis Pregnancy Programme.

- **The number of the eligible risk group to have received 3 doses of HPV vaccine:**
    - **The number of eligible PLHIV to have received 3 doses of HPV vaccine**
    - **The number of eligible MSM to have received 3 doses of HPV vaccine**

4.2 HPV vaccine data collection

The following data should be collected routinely:

- PLHIV (women and men ≤ 26 years, MSM ≤ 45 years)
    - The number of eligible PLHIV receiving first dose
    - The number of eligible PLHIV completing the course
- MSM (≤ 45 years)
    - The number of eligible MSM receiving first dose
    - The number of eligible MSM completing the course

4.3 HPV vaccine reporting form

A HPV vaccine monitoring form has been developed to pilot monitoring of vaccination uptake and completion, see **Appendix 2**.

Monitoring reports should be completed every quarter and sent to Caroline Hurley, Project Manager, HSE Sexual Health & Crisis Pregnancy Programme at caroline.hurley1@hse.ie .

4.4 Further data collection

As part of the evaluation of the roll out of HPV vaccine to at risk groups, further data will be considered for audit at a later stage. This includes:

- PLHIV
    - The number of eligible PLHIV attended
    - The number of males and females previously vaccinated
    - The number of eligible PLHIV offered vaccination
    - The number of eligible PLHIV declining vaccination
    - Reasons for declining vaccination

- MSM
    - The number of eligible MSM attended
    - The number of MSM previously vaccinated
    - The number of eligible MSM offered vaccination
    - The number of eligible MSM declining vaccination
    - Reasons for declining vaccination
- A voluntary, anonymous service user questionnaire may be developed and coordinated by the HSE Sexual Health & Crisis Pregnancy Programme to assess acceptability.

5. Patient information

Patient Information Leaflets about the HPV vaccine have been developed for:

- Men and Women Living with HIV
- Parents of Children Living with HIV
- Men who have Sex with Men (MSM)

Clinics are encouraged to supply patient information leaflets to patients when they are offered the HPV vaccination.

Leaflets can be downloaded from https://www.sexualwellbeing.ie/sexual-health/vaccinations/human-papillomavirus-hpv/ or copies can be ordered through www.healthpromotion.ie.

Appendix 1. Evidence to support extension of HPV vaccination to PLHIV and MSM in Ireland

1. HPV and HPV associated diseases in at risk groups

1.1 PLHIV

Men and women with HIV infection show an increased risk and rate of HPV acquisition and persistence, frequent carriage of multiple HPV types, and an increased risk of HPV-related disease including rapidly progressive malignancies.

HPV carriage rates and overall disease risk increase at low CD4 cell counts. However, despite effective ART, HIV-positive men and women remain disproportionately affected by HPV-related anogenital disease compared with HIV-negative individuals. Among HIV-positive women aged 13-45 years in the United States, Brazil, and South Africa, the overall prevalence of HPV-16 is 32% and HPV-18 is 20% [1].

The prevalence of anal HPV infection in MSM is higher than that observed in heterosexual men (47.2% versus 12.2%) [2]. The prevalence of high risk (HR) or oncogenic anal HPV infection is documented at 26-73% in HIV negative MSM [3, 4] [5]. Prevalence of HR HPV has been shown to be significantly higher in HIV-infected MSM compared to HIV negative MSM with prevalence reported at up to 93% [6] [7] [8]. Receptive anal intercourse, number of sexual partners in the preceding 6 months and HIV infection have been identified as independent predictors of anal HPV infection [9, 10]. Prevalence of oropharyngeal and genital HPV infection has also been reported at significant rates (up to 45%) in MSM and HIV-infected MSM [11] [12].

Persistence of HR HPV infection is the most important factor associated with anal cancer. MSM are frequently found to have multiple concurrent HPV infections in the anal canal. The most oncogenic HR HPV type 16 has been identified as the most likely HPV type to persist over time [13].
Given that prevalence of HR HPV is more common in HIV-infected MSM and rates of clearance are decreased, it is not surprising that persistence of anal HPV in HIV-infected individuals is higher compared to HIV negative individuals [11] [14].

Anal squamous cell cancer (ASCC) accounts for 80% of all anal cancers. ASCC is a relatively rare occurrence in the general population with a reported incidence of 1-2 cases per 100 000 [15], however certain risk groups such as MSM and HIV-infected MSM are disproportionately affected. The incidence of anal cancer in MSM is reported at up to 40 cases per 100 000 [16] with up to 135 cases per 100 000 reported in HIV-infected MSM [13, 15].

The incidence of anal cancer reported in the general population in Ireland from 2006-2013 ranges from 0.8 per 100,000 to 1.2 cases per 100,000. The crude incidence of anal cancer in HIV-infected individuals attending the Department of Genitourinary medicine and Infectious Diseases (GUIDE), St James Hospital is estimated at 44 cases per 100,000 patient years of follow up. Observed incidence was highest in HIV-infected MSM at 49 cases per 100,000 *(personal communication, Dr Corinna Sadlier).*

Similar to findings with other HPV associated malignancies, prevalence of Head and Neck Squamous cell cancer (HNSCC) is higher in PLHIV compared to the general population [17] [18]. The incidence of HNSCC is reported at 2-3 fold higher in PLHIV [19].

Invasive penile cancer is rare. Over a third of penile cancer is associated with HPV, most commonly HPV type 16 and 18 [20]. The risk of penile cancer is up to four fold greater in HIV infected men compared to the general population [18].

A study of HR HPV in women in Ireland found the prevalence of HR HPV to be 51% in women living with HIV versus 19.8% in the general population [21]. Furthermore, an audit of cervical cytology in women living with HIV at GUIDE, Dublin in 2015 found higher rates of abnormalities in women living with HIV compared to the general screened population.

Compared to the screened general population, the frequency of atypical squamous cells of uncertain significance (ASCUS) was 5.5% (versus 3.4%), low-grade squamous intraepithelial lesion (LSIL) 7.2% (versus 3.26%) and high-grade squamous intraepithelial lesion (HSIL) 1.5% (versus 1.09%) *(personal communication, Dr Fiona Lyons).*

1.2 MSM

MSM are at increased risk of HPV infection and HPV associated disease [22]. HPV is causally associated with 80-85% of anal cancers, 36% of oropharyngeal cancer and almost 50% of penile cancers [23] [24].

MSM are disproportionately affected by HPV infection, HPV associated disease including cancer, particularly HPV 16 associated cancers [4] [25]. Rates of anal cancer are 15 times higher in MSM compared to heterosexual men (OR 17.3; 95%CI 8.2 to 36.1) [26] and are comparable to the rates of cervical cancer in women prior to the introduction of the cervical cancer screening programme. Recent data from the Netherlands show a high prevalence (9.4% and 23.9% in HIV negative and positive MSM; with median ages of 38 and 47 years respectively), incidence (8.1% 6 month incidence) and persistence (36.9%) of oral, high risk HPV infection in MSM [27].

2. Safety and efficacy of HPV vaccine in at risk groups

2.1 PLHIV

In studies of quadrivalent HPV vaccine (4vHPV), vaccination has been shown to be safe and immunogenic in HIV-positive children[28] [29]; females aged 16-23 years[30] , 18-25 years [31], or 13-45 years[1]; males aged 22-61 years[32]; and males and females aged 13-27 years[33] . Overall seroconversion rates are high in all groups, and both seroconversion rates and antibody titres are higher than with natural infection, and highest in those receiving antiretroviral therapy (ART) and showing high CD4 cell counts and a suppressed viral load.

A single study has indicated that if the HPV vaccine proved efficacious in the HIV-positive population against vaccine sub-types, the potential reduction in anal cancer rates could be up to 61% [34].

2.2 MSM

In MSM, HPV vaccine is highly immunogenic, prevents new HPV infection and reduces persistent infection, incidence of genital warts and rates of anal intraepithelial neoplasia (AIN) [35] [36] . In MSM without evidence of previous infection 4vHPV vaccination resulted in seroconversion to the four relevant types in 89.7 – 97.4% of individuals. Vaccination is effective in preventing persistent infection of all four types: 78.6 -95.8% in the per-protocol analysis and 55.2-57.5% in the intention to treat analysis [36] [37].

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