South African National Department of Health
Review Report

TITLE: Imiquimod topical (5%) in Anogenital Warts (AGWs)

Date: 13 April 2021 (Initial Review)

Research question: How efficacious is Imiquimod in the treatment of AGWs?

Key findings

- Anogenital warts are caused mainly (90%) by human papillomavirus HPV type 6 and 11 occurring in both male and females.
- Treatments are divided into (1) provider initiated, (2) patient-applied therapy and (3) surgical options. Podophyllin, interferon (IFN) and bi and tri-chloroacetic acid (BCA, TCA) are examples of provider-applied treatments. Patient-applied medications include podophyllotoxin, imiquimod, catechins and 5-fluorouracil (5-FU) cream.
- A Cochrane Review by Grillo-Ardila et al, 2014 and two trials were included in this review of efficacy and safety of imiquimod
- Grillo-Ardila et al, 2014 included the following comparisons: imiquimod vs placebo (6 trials, N=1294), imiquimod vs any other patient-applied treatment (podophyllotoxin and podophyllin) (2 trials, n=105), imiquimod vs provider-administered treatment (ablative methods & cryotherapy) (2 trials, n=335). 1 RCT compared imiquimod (n=65) to placebo n=35) and the remaining RCT compared imiquimod (n=44) to Mycobacterium (Mw) vaccine.
- There was little to no difference in effects for regression of warts or recurrence of warts or safety comparing imiquimod to placebo (low certainty evidence due to very small sample sizes and low event rates).
- We are uncertain about the effect of imiquimod compared to any other patient applied treatment (podophyllotoxin and podophyllin) (2 trials, n=105, very low certainty evidence) or provider-administered treatment (ablative methods & cryotherapy) (2 trials, n=335, very low certainty evidence) respectively.
- Imiquimod may lead to more adverse reactions compared to placebo.
- The RCT by Kumar *et al*., 2014 reported remission/ clearance in 26/44 (59%) in the imiquimod group vs 30/45 (67%) in the Intralesional Mycobacterium vaccine (Mw group).

BACKGROUND

Anogenital warts (AGWs) are caused mainly (90%) by human papillomavirus HPV type 6 and 11 occurring in both male and females. Information regarding the epidemiology of AGWs, in South Africa and other parts of Sub-Saharan Africa, is limited due to the few studies that have been conducted. Banura et al (2013)[1] report studies from high income countries showing the clinical burden of the condition increasing over the years. It is estimated in these regions that approximately 0.5-1.0% of adults below 50 years have AGWs.[1]

AGWs are very infectious with approximately 65% of individuals developing lesions within 3 weeks after exposure to an infected partner. The warts appear as painless benign lesions visible as a lump or raised plaque in the anogenital area. Irritation, bleeding, and emotional distress commonly accompany AGWs. [1]

Treatments are divided into (1) provider initiated, (2) patient-applied therapy and (3) surgical options. Podophyllin, interferon (IFN) and bi and tri-chloroacetic acid (BCA, TCA) are examples of provider-applied treatments. Patient-applied medications include podophyllotoxin, imiquimod, catechins and 5-fluorouracil (5-FU) cream. Imiquimod is indicated for the treatment of external AGW, superficial basal cell carcinoma and actinic keratoses. It has the potential to treat other HPV-associated conditions such as flat warts, plantar warts, and common warts (Verruca vulgaris). Surgical treatments include electrosurgery, surgical excision, cryotherapy, and laser surgery.

In May 2018 the Adult Hospital Level Expert Review Committee, due to supply chain issues with the recommended podophyllin 20%, reviewed alternative topical treatments (TCA and Imiquimod 5%) for AGWs at secondary hospital level for adult patients. A lack of data was reported with respect to comparative effectiveness of the three interventions and the potential advantages and disadvantages of each intervention was reported as unclear. RCTs

identified were small, lacked statistical rigor and clear outcomes. The Committee also noted that it was difficult to discern bias in the studies.[2]

The Committee therefore recommended the following: "*based on the low quality of evidence for products other than podophyllin, the Adult Hospital Level Committee recommends podophyllotoxin 0.5% for clearance of ano-genital warts. However, due to limited availability of this product, the current recommendation of the extemporaneous preparation of podophyllin 20% in compound benzoin tincture BP be retained in the STG and EML."*[2]

The Tertiary ERC is revisiting the review to assess the evidence and use of Imiquimod for tertiary level of care in South Africa, for use in cases refractory to current standard of care.

Introduction

Imiquimod, is United States Food and Drug Administration-approved for treatment of external genital and perianal warts/ condyloma acuminata in patients 12 years or older. For external genital/perianal warts the cream should be applied 3 times per week until total wart clearance or continue use for a maximum of 16 weeks. The 3 times a week dosing includes administration on non-consecutive days e.g.: Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. Ideally, the cream should be applied prior to normal sleeping hours and left on for 6-10 hours. After the 6-to-10-hour application the area can be washed off with mild soap and water. Patients should be advised to wash their hands before and after application.[3]

Objective

We aim to review the use of imiquimod for anogenital warts in adults for potential use at tertiary level, comparing the option of Imiquimod to all other topical and surgical options.

METHODS

We conducted a review by systematically searching PubMed, the Cochrane database and Epistemonikas on 15th January 2021. We restricted the search to randomised control trials and systematic reviews and meta-analyses. We excluded observational studies, case reports, case control, case series, and narrative reviews. Screening of records was done independently and in duplicate (JR & MR), with disagreement resolved through discussion. We compared RCTs between systematic reviews to ensure that there was no duplication and that if we excluded a systematic review relevant RCTs were included independently. Non-English publications were excluded during the review process as feasibility of translations is limited. The search strategy is shown in Appendix 1.

Eligibility criteria for review

Population: Patients (adult and paediatric) with clinically diagnosed anogenital warts (irrespective of biopsy confirmation) where Podophyllin and Salicylic acid treatment has failed

Intervention: Imiquimod topical (5%)

Comparators:

- Placebo
- Podophyllin (0.5%)
- Salicylic acid
- Zinc Sulphate
- Trichloroacetic acid (TCAA)
- Cryotherapy using liquid nitrogen
- Carbon dioxide (CO2) laser therapy
- Freezing and cutting out the AGWs under a local anaesthetic
- Combination of ablative treatment
- Electrotherapy techniques use high-frequency electrical currents to cauterise lesions. There are two types of electrotherapy: electrocautery (also referred to as hyfrecation) and electrical surgery

- Surgical excision
- Any other treatment for AGWs

Outcomes:

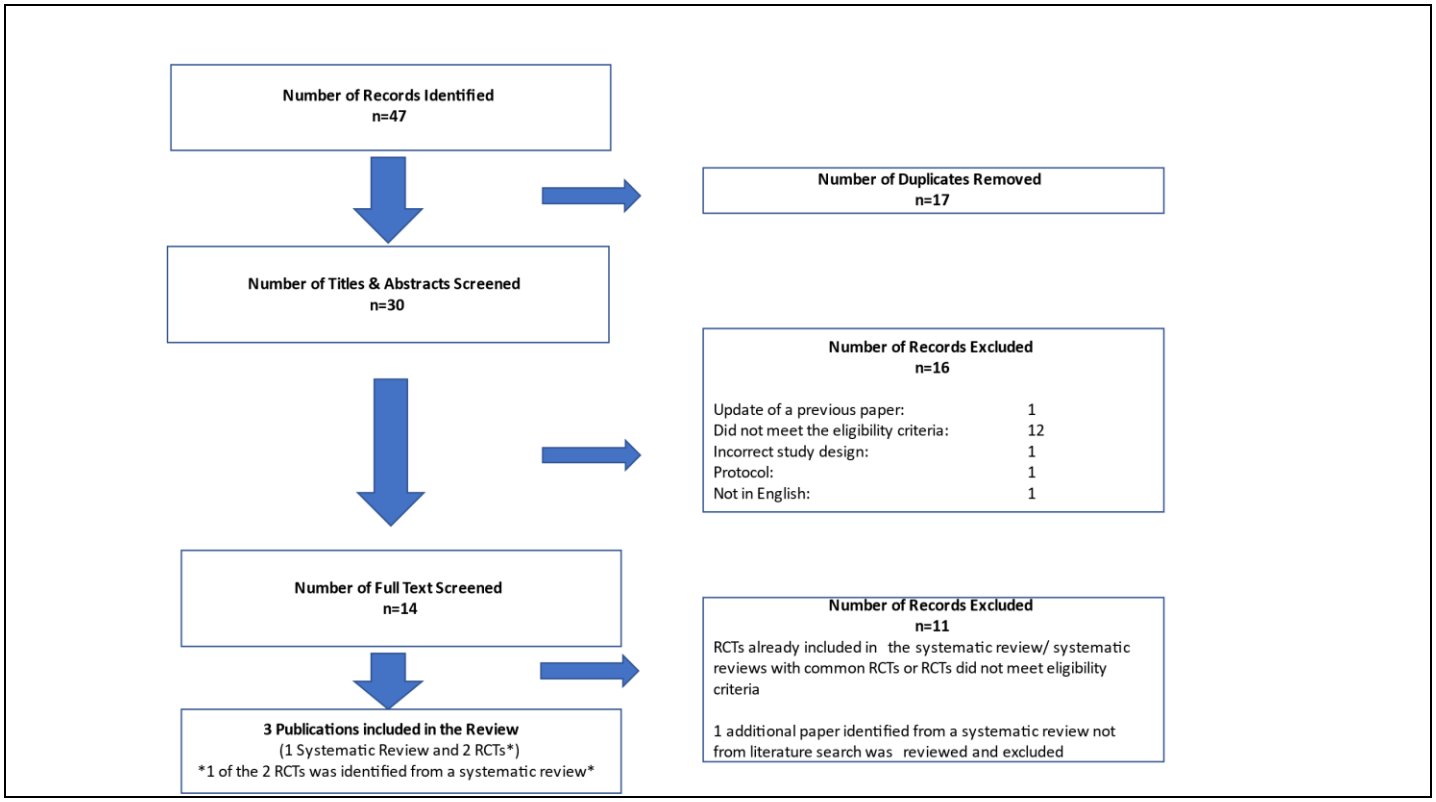
- Wart Healing (Complete clearance/regression at end of treatment)
- Partial clearance/ regression (at least 50% clearance of the lesions),
- Complete clearance at other time points, rate of recurrence,
- Time to complete clearance, volume of clearance,
- Appearance of new AGWs during treatment,
- Adverse events (local adverse reactions during therapy e.g., erythema, irritation, ulceration, erosion, oedema, flaking or induration)

RESULTS

Results of search

The search identified 47 studies. After the removal of 17 duplicates, 30 titles and abstracts were screened. Sixteen records were excluded. Fourteen full text records were reviewed. Twelve records were excluded. One systematic review and 1 RCT were set aside for the review. After comparing studies between systematic reviews, we identified one RCT that was not included in the updated systematic review and included that RCT in our review. Therefore 1 systematic review and 2 RCTs were included in this review.

Figure 1: Prisma Diagram of Selection of Studies



Description of the studies

Data in Table 2 reports the main characteristics and outcomes of the included studies.

Grillo-Ardila et al, 2014[4] of 10 RCTs (n=1734) reviewed imiquimod vs placebo (n=1294, 6 trials), imiquimod vs other patient-applied treatment (podophyllotoxin & podophyllin) (n=105, 2 trials) and imiquimod vs provider-administered treatment (ablative methods & cryotherapy) (n=335, 2 trials) in men & women 18 years and older.

Effectiveness of the intervention

Comparison 1. Imiquimod vs Placebo (n=1294, 6 trials)

- **Regression:** Imiquimod may achieve ***complete*** (RR 4.03, 95% CI 2.03 to 7.99) & ***partial regression*** (RR 2.56, 95% CI 2.05 to 3.20) (Very low-certainty evidence)
- **Recurrence and Appearance of New Warts:** The effect of imiquimod on the rate of recurrence is uncertain (RR 2.76, 95% CI 0.70 to 10.91), imiquimod may reduce the appearance of new warts compared to placebo (RR: 0.76, 95% CI 0.58 to 1.00) (Very low-certainty evidence)
- **Frequency of systemic adverse reactions:** we are uncertain about the effect of Imiquimod on systematic adverse reactions compared to placebo (RR 0.91, 95% CI 0.63 to 1.32) (very low-certainty evidence)
- **Local adverse reactions**: Imiquimod may lead to more adverse reactions compared to placebo (RR 1.73, 95% CI 1.18 to 2.53, low certainty evidence)
- Imiquimod may increase **pain** compared to placebo (RR 11.84, 95% CI 3.36 to 41.63, low certainty evidence)

Comparison 2. Imiquimod vs any other patient-applied treatment (podophyllotoxin and podophyllin) (n=105, 2 trials)

- **Regression:** ***Complete*** (RR 1.09, 95% CI 0.80 to 1.48), & ***partial regression*** (RR 0.77, 95% CI 0.40 to 1.47) (very low quality)
- **Recurrence:** (RR 0.49, 95% CI 0.21 to 1.11) (low quality evidence)
- **Presence of local adverse reactions** (RR 1.24, 95% CI 1.00 to 1.54) (low quality evidence)
- **Systemic adverse reactions** may be less frequent with imiquimod compared to any other patient applied treatment (RR 0.30, 95% CI 0.09 to 0.98) (low quality evidence)

Comparison 3. Imiquimod vs provider-administered treatment (ablative methods & cryotherapy) (n=335, 2 trials)

- **Regression:** Imiquimod may have little or no effect on the frequency of ***complete regression*** (RR 0.84, 95% CI 0.56 to 1.28, Very low-quality evidence)
- **Recurrence:** Imiquimod may lead to a lower rate of recurrence during six-month follow-up (RR 0.24, 95% CI 0.10 to 0.56) but may have little or no effect on recurrence from 6 to 12 months compared to provider-administered treatment (RR 0.71, 95% CI 0.40 to 1.25) (very low-quality evidence)
- **Pain:** we are uncertain about the impact on pain, which may be reduced when imiquimod is used compared to provider-administered treatment (RR 0.30, 95% CI 0.17 to 0.54) - very low quality of evidence
- **Local reactions:** we are uncertain about the effect of Imiquimod compared provider-initiated treatment on local reactions (RR 0.55, 95% CI 0.40 to 0.74) (very low quality of evidence)

HIV infected sub-population

Gilson et al., 1999[5] conducted a prospective, randomized, double-blind, vehicle-controlled study of imiquimod 5% cream or placebo applied for 8 ± 2 hours three times per week for a maximum of 16 weeks in HIV-seropositive males (n = 97) and females (n = 3) aged ≥18 years with clinically diagnosed external anogenital warts, CD4 T lymphocyte count of ≥ 100 $x10^6$ cells/l and Karnofsky score ≥ 70 (higher scores indicate that the patient is better able to carry out daily activities).

Comparison 4. Imiquimod 5% cream (n = 65) vs vehicle (placebo) (n = 35)

Safety:

- Local Skin Reaction: Erythema, (41.9% in Imiquimod group vs 26.7% in the placebo group)
- At least one adverse event (reported by patient) 69.2 vs 65.7%,
- Drug-related adverse effects observed regarding HIV disease between treatment groups

Clearance:

- No significant difference between treatment groups in the number of patients who totally cleared their baseline warts
- Intention to treat analysis showed:
    - Clearance: Imiquimod ((n=7) 11% versus placebo (n=2) 6%, P = 0.488)
    - ≥50% reduction in baseline wart area (38% vs14%, P = 0.013)

New warts

- Imiquimod (12/ 62) (19%) vs (7/30) (23%) patients (P = 0.784) developed new warts
- 3/12 (25%) in imiquimod group cleared new warts vs 0/ 7 (0%) patients in the placebo group.

Other: Intralesional Mycobacterium (Mw) vaccine
Kumar et al., 2014[6] conducted a double-blind randomized clinical trial comparing imiquimod, 5%, cream (n=44) to Intralesional Mycobacterium (Mw) vaccine (n=45) in New Delhi, India.

Comparison 5. Imiquimod 5% cream (n = 65) vs Intralesional Mycobacterium (Mw) vaccine) (n = 44)
Remission/Resolution/Complete Clearance

- 26 (59%) in the imiquimod group vs 30 (67%) in Mw group

% Reduction in the Surface Area of AGWs
≥75% but <100% resolution

- 9 (20%) in the imiquimod group vs 7 (16%) in the Mw group

< 75% resolution to no response or worsening

- 9 (20%) in the imiquimod group vs 8 (18%) in the Mw group

Mean Resolution of AGWs
85% in the imiquimod group vs 83% in the Mw group

% Reduction in viral load for HPV-6 and HPV-11

- Mw: Significant decline in mean viral loads of HPV-6 (P = 0.003) & HPV-11 (P = 0.03) in the Mw group vs significant decline in viral load of HPV-6 only (P = 0.01) in the imiquimod group

CONCLUSION

Imiquimod may not be superior in improving clinical outcomes or be safer compared to placebo, patient applied treatment (podophyllotoxin and podophyllin), provider-administered ablative methods & cryotherapy and intralesional Mycobacterium vaccine. The evidence is lacking to clarify whether imiquimod makes a difference to clinical and safety outcomes or not. The included review was of good quality. However, the included trials were small and may have been underpowered. The data reviewed does not confirm the superiority of imiquimod in the management of AGW. The evidence shows that there might be no difference in regression, resolution, or safety for imiquimod compared to other treatments.

Reviewer(s): Dr J Riddin, Dr M Reddy

Declaration of interests: JR (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme) and MR (Better Health Programme, South Africa), have no interests to declare.

Acknowledgements: Tamara Kredo and Ameeth Hohlfeld Cochrane South Africa, South African Medical Research.

Table 1: Excluded studies

No	Citation	Reason for Exclusion
1	Murray ML, Meadows J, Doré CJ, Copas AJ, Haddow LJ, Lacey C, Jit M, Soldan K, Bennett K, Tetlow M, Nathan M, Gilson R. Human papillomavirus infection: protocol for a randomised controlled trial of imiquimod cream (5%) versus podophyllotoxin cream (0.15%), in combination with quadrivalent human papillomavirus or control vaccination in the treatment and prevention of recurrence of anogenital warts (HIPvac trial). BMC Med Res Methodol. 2018 Nov 6;18(1):125. doi: 10.1186/s12874-018-0581-z. PMID: 30400777; PMCID: PMC6220496.	A protocol
2	Barton S, Wakefield V, O'Mahony C, Edwards S. Effectiveness of topical and ablative therapies in treatment of anogenital warts: a systematic review and network meta-analysis. BMJ Open. 2019 Oct 31;9(10):e027765. doi: 10.1136/bmjopen-2018-027765. PMID: 31676644; PMCID: PMC6830637.	Papers included in the Cochrane Review. Paper not included in the Cochrane review, reviewed independently
3	Werner RN, Westfechtel L, Dressler C, Nast A. Anogenital warts and other HPV- associated anogenital lesions in the HIV-positive patient: a systematic review and meta-analysis of the efficacy and safety of interventions assessed in controlled clinical trials. Sex Transm Infect. 2017 Dec;93(8):543-550. doi: 10.1136/sextrans-2016-053035. Epub 2017 Jun 21. PMID: 28637906.	Did not meet PICO
4	Komericki P, Akkilic-Materna M, Strimitzer T, Aberer W. Efficacy and safety of imiquimod versus podophyllotoxin in the treatment of anogenital warts. Sex Transm Dis. 2011 Mar;38(3):216-8. doi: 10.1097/OLQ.0b013e3181f68ebb. PMID: 20938374.	In the Cochrane Review
5	Ciavattini A, Tsiroglou D, Vichi M, Di Giuseppe J, Cecchi S, Tranquilli AL.Topical Imiquimod 5% cream therapy for external anogenital warts in pregnant women: report of four cases and review of the literature. J Matern Fetal Neonatal Med. 2012 Jul;25(7):873-6. doi: 10.3109/14767058.2011.600795. Epub 2011 Aug 18. PMID: 21815878.	Incorrect Study Design
6	Feng C, Li W, Wang X, Zhang H, Si L, Chen Z, Bai M. A systematic review evaluating the efficacy and safety of a combination of ablative treatment and self administered treatment versus ablative treatment alone for external anogenital warts. Int J Dermatol. 2020 Oct;59(10):1210-1216. doi: 10.1111/ijd.14863. Epub 2020 Apr 16. PMID: 32297994.	Did not meet PICO
7	Bertolotti A, Milpied B, Fouéré S, Dupin N, Cabié A, Derancourt C. Local Management of Anogenital Warts in Non-immunocompromised Adults: A Systematic Review and Meta-analyses of Randomized Controlled Trials. Dermatol Ther (Heidelb). 2019 Dec;9(4):761-774. doi: 10.1007/s13555-019-00328-z. Epub 2019 Oct 13. PMID: 31606873; PMCID: PMC6828858.	All but one article included in the Cochrane Review. The One appliable RCT was reviewed independently
8	Werner RN, Westfechtel L, Dressler C, Nast A. Self-administered interventions for anogenital warts in immunocompetent patients: a systematic review and meta-analysis. Sex Transm Infect. 2017 May;93(3):155-161. doi: 10.1136/sextrans-2016-052768. Epub 2016 Nov 1. PMID: 27803240.	Included in the Cochrane Review
9	Baker DA, Ferris DG, Martens MG, Fife KH, Tyring SK, Edwards L, Nelson A, Ault K, Trofatter KF, Liu T, Levy S, Wu J. Imiquimod 3.75% cream applied daily to treat anogenital warts: combined results from women in two randomized, placebo-controlled studies. Infect Dis Obstet Gynecol. 2011;2011:806105. doi: 10.1155/2011/806105. Epub 2011 Aug 24. PMID: 21876641; PMCID: PMC3162968.	Did not meet PICO
10	Tzellos TG, Sardeli C, Lallas A, Papazisis G, Chourdakis M, Kouvelas D. Efficacy, safety and tolerability of green tea catechins in the treatment of external anogenital warts: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2011 Mar;25(3):345-53. doi: 10.1111/j.1468-3083.2010.03796.x. PMID: 21294779.	Did not meet PICO
11	W Buck H Jr. Warts (genital). BMJ Clin Evid. 2010 Aug 13;2010:1602. PMID: 21418685; PMCID: PMC3217761.	Relevant papers already included in the Cochrane Review
12	Stefanaki C, Katzouranis I, Lagogianni E, Hadjivassiliou M, Nicolaidou E, Panagiotopoulos A, Anyfantakis V, Bethimoutis G, Rallis E, Antoniou C, Katsambas A. Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. Int J STD AIDS. 2008 Jul;19(7):441-4. doi: 10.1258/ijsa.2007.007196.Erratum in: Int J STD AIDS. 2008 Oct;19(10):722. Hagjivassiliou, Maria [corrected to Hadjivassiliou, Maria]; Eustathios, Rallis [corrected to Rallis, Eustathios]. PMID: 18574113.	Included in the Cochrane Review
13	Kumar P, Dar L, Saldiwal S, Varma S, Datt Upadhyay A, Talwar D, Sharma VK, Verma KK, Dwivedi SN, Raj R, Gupta S. Intralesional injection of Mycobacterium w vaccine vs imiquimod, 5%, cream in patients with anogenital warts: a randomized clinical trial. JAMA Dermatol. 2014 Oct;150(10):1072-8. doi: 10.1001/jamadermatol.2014.794. PMID: 25103148.	Did not meet PICO
14	Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, Hougham AJ, Schmitt KA. Self-administered topical 5% imiquimod cream for external anogenital warts. HPV Study Group. Human PapillomaVirus. Arch Dermatol. 1998 Jan;134(1):25-30. doi: 10.1001/archderm.134.1.25. PMID: 9449906.	Included in the Cochrane Review
15	Arican O, Guneri F, Bilgic K, Karaoglu A. Topical imiquimod 5% cream im external anogenital warts: a randomized, double-blind, placebo-controlled study. J Dermatol. 2004 Aug;31(8):627-31. doi: 10.1111/j.1346-8138.2004.tb00568.x. PMID: 15492435.	Included in the Cochrane Review
16	Schöfer H, Van Ophoven A, Henke U, Lenz T, Eul A. Randomized, comparative trial on the sustained efficacy of topical imiquimod 5% cream versus conventional ablative methods in external anogenital warts. Eur J Dermatol. 2006 Nov-Dec;16(6):642-8. PMID: 17229604.	Included in the Cochrane Review

No	Citation	Reason for Exclusion
17	Gotovtseva EP, Kapadia AS, Smolensky MH, Lairson DR. Optimal frequency of imiquimod (aldara) 5% cream for the treatment of external genital warts inimmunocompetent adults: a meta-analysis. Sex Transm Dis. 2008 Apr;35(4):346-51. doi: 10.1097/OLQ.0b013e31815ea8d1. PMID: 18360317.	Included in the Cochrane Review
18	Pelletier F, Drobacheff-Thiebaut C, Aubin F, Venier AG, Mougin C, Laurent R. Effets de l'imiquimod sur l'infection périanale latente à papillomavirus humain chez des malades infectés par le virus de l'immunodéficience humaine [Effects of imiquimod on latent human papillomavirus anal infection in HIV-infected patients]. Ann Dermatol Venereol. 2004 Nov;131(11):947-51. French. doi: 10.1016/s0151-9638(04)93803-3. PMID: 15602380.	Not English Language
19	Tyring SK, Arany I, Stanley MA, Tomai MA, Miller RL, Smith MH, McDermott DJ, Slade HB. A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. J Infect Dis. 1998 Aug;178(2):551-5. doi: 10.1086/517472. PMID: 9697742.	Included in the Cochrane Review
20	Chun Shing Kwok, Sam Gibbs, Cathy Bennett, Richard Holland, Rachel Abbott. Topical treatments for cutaneous warts. Intervention Review 12 September 2012	Did not meet PICO
21	Litha Pepas, Sonali Kaushik, Andy Nordin, Andrew Bryant, Theresa A Lawrie. Medical interventions for high-grade vulval intraepithelial neoplasia. Intervention Review 18 August 2015 Free access	Did not meet PICO
22	Claudio S Batista, Álvaro N Atallah, Humberto Saconato, Edina MK da Silva. 5-FU for genital warts in non-immunocompromised individuals Intervention Review 14 April 2010	Did not meet PICO
23	Antonio Macaya, Carlos Muñoz-Santos, Albert Balaguer, Maria Jesús Barberà. Interventions for anal canal intraepithelial neoplasia Intervention Review 12 December 2012	Did not meet PICO
24	Theresa A Lawrie, Andy Nordin, Manas Chakrabarti, Andrew Bryant, Sonali Kaushik, Litha Pepa. Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia Intervention Review 5 January 2016 Free access	Did not meet PICO
25	Jason Thomson, Sarah Hogan, Jo Leonardi-Bee, Hywel C Williams, Fiona J Bath Hextall. Interventions for basal cell carcinoma of the skin Intervention Review 17 November 2020	Did not meet PICO
26	Rachel Heslop, Helen Roberts, Deralie Flower, Vanessa Jordan. Interventions for men and women with their first episode of genital herpes. Intervention, Review, 30 August 2016. Free access	Did not meet PICO
27	Authors»Ahn CS , Huang WW. Imiquimod in the treatment of cutaneous warts: an evidence-based review. American journal of clinical dermatology Year»2014 Links»Pubmed DOI	Did not meet PICO
28	Bertolotti A, Dupin N, Bouscarat F, Milpied B, Derancourt C. Cryotherapy to treat anogenital warts in nonimmunocompromised adults: Systematic review and meta-analysis. J Am Acad Dermatol. 2017 Sep;77(3):518-526. doi: 10.1016/j.jaad.2017.04.012. Epub 2017 Jun 23. PMID: 28651824.	Did not met PICO

n=47 articles retrieved. n=17 duplicates. n=28 excluded. 2 Papers included and 1 RCT from a systematic review excluded as it contained studies included in the Cochrane Review.

Table 2: Characteristics of reviewed studies

i) Cochrane Reviews:

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Grillo-Ardila et al, 2014[4]	Systematic review of 10 RCTs (n=1734) 6 trials (n=1294) imiquimod vs placebo 2 trials (n=105) imiquimod vs other patient-applied treatment (podophyllotoxin & podophyllin) 2 trials (n=335) imiquimod vs provider-administered	Men & women aged >18 years old: • 1 trial included participants aged between 15 & 81 years. • 1 trial designed to include people > 12 years old ended up recruiting participants between 26 & 35 years old. • 2 trials included only men or women AGW regardless of: • location • shape • size • number • compromised area: except for 5 trials	Imiquimod (any concentration, frequency & duration) versus: • placebo • expectant management • other patient-applied treatment such as podofilox or catechins (any concentration, frequency & duration) • other provider-administered treatment such as bi &	**Primary outcomes** 1. Complete regression 2. Partial regression (at least 50% clearance) 3. Dyspareunia **Secondary outcomes** 1. Time to complete regression 2. Relief of symptoms during treatment 3. Recurrence during follow-up (0 to 6 months, & 6 to 12 months) 4. Appearance of new warts during treatment 5. Excessive scarring at application site (hypertrophic scar or keloid)	***Imiquimod vs placebo:*** very low- or low-quality evidence for the following outcomes: ***Complete and partial regression:*** Complete (RR 4.03, 95% CI 2.03 to 7.99) & partial regression (RR 2.56, 95% CI 2.05 to 3.20) ***Recurrence:*** (RR 2.76, 95% CI 0.70 to 10.91) ***Appearance of new warts:*** (RR: 0.76, 95% CI 0.58 to 1.00)	AMSTAR assessment of the systematic review: **HIGH Quality Review** 1. Research questions and inclusion criteria for the review included the components of PICO? **Yes** 2. Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? **Partial Yes** 3. Review authors explained selection of the study designs for inclusion in the review? **Yes**

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
	treatment (ablative methods & cryotherapy)	○ 1 limited the compromised area to 20 cm^2 ○ 3 used the number of AGW lesions as an inclusion criteria: ▪ between 2 & 30 between ▪ 2 & 50 • Previous Treatment: ○ 7 history of treatment ○ 2 included naïve population ○ 1 did not mention previous treatment	• tri-chloroacetic acid (TCA & BCA) • cryotherapy or surgical removal (any concentration, frequency & duration). Interferon and 5-FU were excluded	6. Time to resumption of intercourse 7. Pain during therapy 8. Pigmentary changes at application site (hypo- or hyperpigmentation at the site of application) 9. Any local adverse reactions during therapy 10. Any systemic adverse reactions during therapy 11.Requirement of any additional patient-applied or provider administered treatment at the end of therapy 12.Patient's satisfaction 13.Cost effectiveness of imiquimod	***Frequency of systemic adverse reactions:*** (RR 0.91, 95% CI 0.63 to 1.32) ***Local Adverse Reactions:*** Imiquimod led to more local adverse reactions (RR 1.73, 95% CI 1.18 to 2.53) ***Pain:*** (RR 11.84, 95% CI 3.36 to 41.63). ***Imiquimod versus any other patient-applied treatment (podophyllotoxin & podophyllin):*** Imprecise (low & very low-quality evidence). ***Complete & partial regression:*** Complete (RR 1.09, 95% CI 0.80 to 1.48), partial regression (RR 0.77, 95% CI 0.40 to 1.47) ***Recurrence:*** (RR 0.49, 95% CI 0.21 to 1.11) ***Presence of local adverse reactions:*** (RR 1.24, 95% CI 1.00 to 1.54) ***Systemic adverse reactions*** were less frequent with imiquimod (RR 0.30, 95% CI 0.09 to 0.98). ***Imiquimod vs any other provider-administered treatment (ablative methods and cryotherapy):*** Very low quality of evidence ***Complete regression:*** Imiquimod did not have a lower frequency of	4. Review authors used a comprehensive literature search strategy? **Partial Yes** 5. Review authors perform study selection and data extraction in duplicate? **Yes** 6. Review authors provided a list of excluded studies and justify the exclusions? **Yes** 7. Review authors described the included studies in adequate detail? **Yes** 8. Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **Yes** 9. Review authors reported on the sources of funding for the studies included in the review? **Yes** **10.** For meta-analyses, review authors used appropriate methods for statistical combination of results? **Yes** 11. For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis? **Yes** 12. Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review? **Yes** 13. Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? **Yes** 14. For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review? **Yes**

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
					complete regression (RR 0.84, 95% CI 0.56 to 1.28). ***Recurrence:*** Imiquimod led to a lower rate of recurrence during 6-month follow-up (RR 0.24, 95% CI 0.10 to 0.56) but not a lower recurrence from 6 to 12 months (RR 0.71, 95% CI 0.40 to 1.25) **Pain:** (RR 0.30, 95% CI 0.17 to 0.54) ***Local Reactions:*** Fewer with imiquimod (RR 0.55, 95% CI 0.40 to 0.74).	15. Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review? **Yes** Risk of Bias in the 10 Trials: **HIGH RISK** due to lack of blinding, failure to adhere to the intention-to-treat principle, selective reporting and other risk of bias such as publication bias because the included trials were mostly funded by industry. Measurement bias was also a concern as some outcomes were assessed subjectively. **Conclusion:** Benefits and harms of imiquimod compared with placebo and other topical treatments of surgery should be regarded with caution due to the risk of bias, imprecision, and inconsistency for many of the outcomes.

ii) Randomised controlled studies:

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes	Quality appraisal
Gilson et al., 1999[5]	Prospective, randomized, double-blind, vehicle-controlled study of imiquimod 5% cream or placebo/vehicle applied for 8 ± 2 hours 3x per week for a maximum of 16 weeks	HIV-seropositive males (n = 97) and females (n = 3) aged ≥18 years with clinically diagnosed external anogenital warts, CD4 T lymphocyte count of ≥ 100 x10^6 cells/l and Karnofsky score ≥ 70. *The Karnofsky Performance Status scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities.*	Imiquimod 5% cream vs placebo/ vehicle Applied for 8 ± 2 h three times per week for a maximum of 16 weeks	• Safety • Wart clearance **Imiquimod (n = 65) vs vehicle (placebo) (n = 35)** • Most common local skin reaction was erythema, (41.9% in Imiquimod group & 26.7% in placebo group) • Incidence of patients reporting at least 1 adverse event was 69.2 & 65.7%, respectively. • No clinically meaningful differences or changes in laboratory values (hematologic and serum chemistry parameters) were observed between treatment groups, • No drug-related adverse effects observed regarding HIV disease between treatment groups • Although no significant difference between treatment groups in the number of patients who totally cleared their baseline warts the intention to treat analysis showed the following: imiquimod ((n=7) 11% vs placebo (n=2) 6%, P = 0.488) totally cleared warts, significantly more imiquimod treated patients experienced a ≥ 50% reduction in baseline wart area (38% versus 14%, P = 0.013) • New warts (warts do not present at the initiation visit) ○ 12/62 (19%) patients in imiquimod group vs 7/ 30 (23%) patients in the placebo group (P = 0.784) developed new warts	Limitations not addressed in paper ***Authors Conclusions:*** Topical imiquimod cream may have clinical utility in treating AGWs in HIV positive patients Small Sample. **Selection Bias:** Randomization - **Low Risk** **Performance Bias:** Double blinding - **Low Risk** **Measurement Bias**: Measurement of Karnofsky performance might be subjective – Moderate to **High Risk** **Attrition bias: High Risk**: 5(8%) in the imiquimod group vs 7 (20%) in the vehicle group were lost to follow-up. >10% lost to follow up can impact study **Overall risk of bias: Unclear Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes	Quality appraisal
				○ 3/12 (25%) patients in the imiquimod group cleared their new warts vs none of the 7 (0%) patients in the placebo group.	
Kumar et al., 2014[6]	Double-blind randomized clinical trial Between February 2009 and July 2012 plus a 3-month follow-up	N= 89 Imiquimod, 5%, cream (n=44) Intralesional Mycobacterium (Mw) vaccine (n=45) New Delhi, India	Imiquimod, 5%, cream Intralesional Mw vaccine	***Primary Outcome:*** Complete clinical remission of visible AGWs ***Secondary Outcomes:*** • % reduction in the surface area of AGWs • % reduction in viral load for HPV-6 and HPV-11 **Remission/Resolution/Complete Clearance** • 26 (59%) in the imiquimod group vs 30 (67%) in Mw group **% Reduction in the Surface Area of AGWs** *≥75% but <100% resolution* • 9 (20%) in the imiquimod group vs 7 (16%) in the Mw group < 75% resolution to no response or worsening • 9 (20%) in the imiquimod group vs 8 (18%) in the Mw group **Mean resolution of AGWs** 85% in the imiquimod group vs 83% in the Mw group **% Reduction in viral load for HPV-6 and HPV-11** **Mw:** Significant decline in mean viral loads of HPV-6 (P = 0.003) & HPV-11 (P = 0.03) **Imiquimod:** Significant decline in viral load of HPV-6 only (P = 0.01)	Limitations not addressed in paper ***Authors Conclusions:*** Although invasive and associated with local immunologic reactions, intralesional Mw vaccine therapy is as effective as imiquimod, 5%, in the treatment of AGWs and results in elimination of HPV in the lesion **Selection Bias:** **Low Risk** - randomization and baseline characteristics did not differ significantly **Performance Bias:** **Low Risk** Double-blind RCT. Investigators (clinical and laboratory), patients, and the biostatistician were blinded for the trial intervention **Attrition bias:** **High Risk**: 3 (7%) in the imiquimod group vs 6 (13%) in the Mw group withdrew, were lost to follow-up, or defaulted before resolution of the AGWs during the treatment phase. 10% loss to follow can impact a small study

Appendix 1: Search strategy

Database:	**PUBMED**
Date:	**15 January 2021**
Search Strategy:	**Imiquimod [MeSH Terms]) AND (anogenital warts [MeSH Terms])**
Number of studies:	**24 studies**
Database:	**Cochrane Database https://www.cochranelibrary.com/**
Date:	**15 January 2021**
Search Strategy:	**Imiquimod and Anogenital Warts**
Number of studies reviews:	**8 reviews**
Database:	**Epistemonikos https://www.epistemonikos.org/**
Date:	**15 January 2021**
Search Strategy:	**Imiquimod and Anogenital Warts**
Number of studies numbers:	**15 articles**

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Three studies were reviewed: **1 Cochrane Review[4] with imprecise to very low- and low-quality evidence** • Imiquimod vs placebo (n=1294, 6 trials), • Imiquimod vs other patient-applied treatment (podophyllotoxin & podophyllin) (n=105, 2 trials) and • Imiquimod vs provider-administered treatment (ablative methods & cryotherapy) (n=335, 2 trials) **2 Small RCTs** • Imiquimod (n=65) vs Placebo(n=35)5 • Imiquimod (n=44) vs Intralesional Mw vaccine(n=45)6

EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?**
	Large [ ] Moderate [ ] Small [X] None [ ]
		***Cochrane Review[4]:* 1. Imiquimod vs Placebo Very low based on imprecise estimates** in terms of regression and recurrence & appearance of new warts:
		
		***RCT By Gilson et al., 1999[5] showed for:* Imiquimod vs Placebo**
		• No significant difference in the total clearance of baseline warts
		• **New warts:**
		  • 12/ 62 (19%) vs 7/30 (23%) (P = 0.784)
		  • 3/12 (25%) vs 0/7 (0%) cleared new warts
		
		Cochrane Review[4]: 2.* Imiquimod vs any other patient-applied treatment (podophyllotoxin and podophyllin) *imprecise evidence for regression and recurrence
		
		Cochrane Review[4]: 3. Imiquimod vs provider-administered treatment (ablative methods & cryotherapy) *Very low-quality evidence* for regression and recurrence
		
		4. Imiquimod vs Intralesional Mycobactrium (Mw) Vaccine[6]
		• **Remission/Resolution/Complete Clearance:** 26 (59%) in the imiquimod group vs 30 (67%) in Mw group

<table>
<tr><td></td><td></td><td>

- **% Reduction in the Surface Area of AGWs**
  - *≥75% but <100% resolution*
    - 9 (20%) in the imiquimod group vs 7 (16%) in the Mw group
  - < 75% resolution to no response or worsening
    - 9 (20%) in the imiquimod group vs 8 (18%) in the Mw group
- **Mean resolution of AGWs** : 85% in the imiquimod group vs 83% in the Mw group
- **% Reduction in viral load for HPV-6 and HPV-11**
  - **Mw:** Significant decline in mean viral loads of HPV-6 (P = 0.003) & HPV-11 (P = 0.03)
  - **Imiquimod:** Significant decline in viral load of HPV-6 only (P = 0.01)

</td></tr>
<tr><td>QUALITY OF EVIDENCE OF HARM</td><td>

What is the certainty/quality of evidence?

High ☐ Moderate ☐ Low ☒ Very low ☐

High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect

</td><td>

1 Cochrane Review[4] with imprecise to very low and low-quality evidence and 2 Small RCTs [5,6]

Limited comparisons

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<tr><td>EVIDENCE OF HARMS</td><td>

What is the size of the effect for harmful outcomes?

Large ☐ Moderate ☐ Small ☒ None ☐

</td><td>

Cochrane Review[4]:* 1. <u>Imiquimod vs Placebo</u> *Very low and imprecise estimates for frequency of systemic reactions systemic adverse reaction, local adverse reactions, and pain

***RCT By Gilson et al., 1999[5] showed for:* Safety:**

- ***Local Skin Reaction:*** Erythema, (41.9% in Imiquimod group vs 26.7% in placebo group)

At least one adverse event 69.2 vs 65.7%,

- ***Drug-related adverse effects*** not observed

Cochrane Review[4]:* 2. <u>Imiquimod vs any other patient-applied treatment (podophyllotoxin and podophyllin)</u> *imprecise evidence for local adverse reactions and systemic adverse reactions

Cochrane Review[4]: 3. <u>Imiquimod vs provider-administered treatment (ablative methods & cryotherapy)</u> (n=335, 2 trials) ***Very low-quality evidence*** for pain and local reactions

</td></tr>
<tr><td>BENEFITS & HARMS</td><td>

Do the desirable effects outweigh the undesirable harms?

Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒

</td><td>

The evidence does not confirm that imiquimod is safer to topical preparations or surgical interventions

</td></tr>
<tr><td>FEASABILITY</td><td>

Is implementation of this recommendation feasible?

Yes ☐ No ☐ Uncertain ☒

</td><td>

Evidence is lacking. It is uncertain if imiquimod is superior to other treatments or to surgical options

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<tr><td>RESOURCE USE</td><td>

How large are the resource requirements?

More intensive ☐ Less intensive ☒ Uncertain ☐

</td><td>

Active Ingredients	Unit	Dosage Form	Pack Size	Single Exit Price**	Unit Price
Imiquimod*	mg	Cream	12	1096,35	91,36

Single Exit Price[7]: December 21st, 2020 Database
**Aldara 5%*
*** Rand*

</td></tr>
</table>

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	No information
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	No risk of health inequity

TERTIARY LEVEL ERC AND NEMLC RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				
Recommendation: It is recommended that imiquimod topical (5%) not be included on the Essential Medicines List for Anogenital Warts (AGWs). **Rationale:** Superiority of imiquimod topical (5%) in terms of efficacy or safety compared to other alternatives cannot be confirmed. **Level of Evidence:** Low evidence available (level I)					

(Refer to appendix 2 for the evidence to decision framework)

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