ANRS EP 57 - APACHES - Information for research participants

Title : ANRS EP57 APACHES Natural history of anal human papillomavirus infection and associated disease in HIV-infected men who have sex with men: towards an evidence base for the prevention of anal cancer

In brief	Investigator: Isabelle ETIENNEY
	Structure/teams : - Centre international de Recherche sur le Cancer (Dr Gary CLIFFORD) - Groupe hospitalier Diaconesses Croix Saint-Simon (Dr Isabelle ETIENNEY)
	Start dates: 2nd December 2014 End date of research: 30th Jun 2022
	Number of participants recruited : 513
	Research status: completed
	Pathology: VIH/CANCER
	Promotion: Inserm - ANRS MIE
	Funded under: AAP 2013-2
The project	Persons living with HIV, particularly men having sex with men, have a high burden of HPV-related anal cancer. At the time of initiation of this study, although screening for anal cancer in persons living with HIV (PLHIV) had been proposed, using cytological, virological or other biomarkers to detect and treat the presumed anal cancer precursor, anal intraepithelial neoplasia (AIN)2/3, very little was known about the natural history of anal HPV infection and AIN2/3, nor about the efficiency of anal screening algorithms. Objectives: To characterise the natural history of anal HPV infection and related lesions among ¬500 HIV-infected homosexual men aged 35 years across France (Paris, Marseille, Lyon, Rennes, dijon and Montpellier), we proposed to: 1) Determine the prevalence, incidence and persistence of type-specific anal HPV DNA and cytological abnormalities. 2) Evaluate markers of transforming HPV infection (HPV type, p16/Ki67 staining) as predictive factors for AIN2/3, confirmed histologically via the use of high-resolution anoscopy (HRA), and their utility as screening tests. 3) Observe the rate of, and characterise predictive markers for, the regression and/or re-occurrence of untreated AIN2/3, followed by regular surveillance. Perspectives: Study results were expected to inform guidelines for anal cancer screening in persons living with HIV in France and elsewhere (which they did - see below).
Latest news	Since publication of APACHES findings, first French recommendations for anal screening have been published (Spindler L, Société Nationale Française de Colo-Proctologie, Tech Coloproctol. 2024), including for persons living with HIV (Recommandations de dépistage et prise en charge des cancers chez les personnes vivant avec le VIH, des hépatites virales et des IST : rapport d'experts, https://cns.sante.fr/wp-content/uploads/2024/06/VIH-Cancer_Recommandation_Rapport-dexperts_-20240521.pdf)
Publication references	Findings from baseline visits: 1) Determinants of high-grade anal intraepithelial lesions in HIV-positive MSM. Clifford GM et al, AIDS. 2018

	2) Prevalence and Risk Factors for Anal Human Papillomavirus Infection in Human Immunodeficiency Virus-Positive Men Who Have Sex with Men. Combes JD et al, J Infect Dis. 2018 Findings from 2 year follow-up: 3) Incidence and Clearance of Anal Human Papillomavirus (HPV)-16 and HPV-18 Infection, and Their Determinants, Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men in France. Alberts CJ, J Infect Dis. 2020 4) Cumulative Detection of Anal High-Grade Squamous Intraepithelial Lesions Over 2-Year Follow-up in Men Who Have Sex With Men Living With Human Immunodeficiency Virus in France. Combes JD et al. J Infect Dis. 2024 Findings from 5-year follow-up of anal HSIL: 5) PERSISTENCE AND CLEARANCE OF HISTOLOGICAL ANAL HIGH-GRADE LESIONS IN MEN WHO HAVE SEX WITH MEN LIVING WITH HIV. Clifford GM et al. Abstract. International Papillomavirus Conference. Edinburgh. 2024. 6) Evolution of Untreated Anal High-grade Squamous Intraepithelial Lesions in High-risk Men: A Prospective 5-year Clinical Follow-up in the ANRS-EP57-APACHES study. Etienney I, Clifford GM et al. Clin Infect Dis. 2026 Aug 14:ciag477. doi: 10.1093/cid/ciag477 - https://pubmed.ncbi.nlm.nih.gov/42600099/ Contribution of baseline data to larger pooled analyses: 7) Incidence and Clearance of Anal Human Papillomavirus Infection in 16 164 Individuals, According to Human Immunodeficiency Virus Status, Sex, and Male Sexuality: An International Pooled Analysis of 34 Longitudinal Studies. Wei F, et al. Clin Infect Dis. 2023 8) Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Wei F et al Lancet HIV. 2021 9) A systematic review and meta-analysis of cytology and HPV-related biomarkers for anal cancer screening among different risk groups. Clarke MA, Int J Cancer. 2022
Main objectives	To characterise the natural history of anal HPV infection and related lesions among HIV-infected homosexual men aged 35 years across France.
Secondary objectives	- Assess the frequency of spontaneous regression of high-grade anal lesions. - Evaluate markers predictive of detection and regression of high-grade anal lesions and their utility as screening tests. - Assess the prevalence, incidence and persistence of anal HPV infection.
Optional: Link to research website	NA

Website filter management ***(Part to be deleted when versioning for publication - for use by the communications department for layout purposes only)***

Select the categories that will be used to classify the Project File for the filter search on the website (Select the items for each filter).

Type of infection	**Withdrawals**
☐Covid-19	☒DNA (from anal cytology samples)
☒IST (Human Papillomavirus)	☒RNA (from anal cytology samples)
☐Tuberculous meningitis	☐DBS
☐Mpox	☐Nasopharyngeal and oropharyngeal swab
☐Tuberculosis	☐PBMC (-80°C)
☐VHB	☐PBMC
☐HCV	☐Plasma
☐VHD	☐Saliva
☒HIV-1	☐Whole blood
☒HIV-2	☐Serum
☐Healthy volunteer	☐Urine
	☒Other sampling (Anal cells)

Population
☐Teens
☒Adults
☐Children

COUNTRY
☐ Brazil
☐ Burkina Faso
☐ Cambodia
☐ Cameroon
☐ Ivory Coast
☐ Egypt
☐ Europe
☒ France
☐ Guinea
☐ Mali

☐ RDC ☐ Senegal ☐ Vietnam ☐ Zambia
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A - Overall research results

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A - Overall research results Details of study results are reported in the publications below. However, the principal findings that have directly influenced clinical practice and have been captured in new recommendations for anal screening, including in MSM persons living with HIV (Spindler L, Société Nationale Française de Colo-Proctologie, Tech Coloproctol. 2024), and HIV management guidelines ( ) are the following :

1) Not all anal high-grade lesions are true anal pre-cancers, and if left untreated, a majority will regress. Thus, the number of unnecessary interventions in PLHIV, and the efficiency of anal screening programs, especially given the complexity and limited capacity of high-resolution anoscopy, can be improved by markers that identify the subset of HSIL that will persist and are most likely to evolve to anal cancer.
2) HPV16 infection, by far the most carcinogenic HPV type in the anus, appears to be a strong determinant of anal high-grade lesions and their evolution, and is hence an efficient triage tool for anal cancer screening programs.

Summary of results (CMG initiates and PI links→ ANRS validation)

Publication references

1. Cumulative Detection of Anal High-Grade Squamous Intraepithelial Lesions Over 2-Year Follow-up in Men Who Have Sex With Men Living With Human Immunodeficiency Virus in France. Combes JD, Didelot JM, Radenne S, Zaegel-Faucher O, Lesage AC, Siproudhis L, Piroth L, Marchand L, Heard I, Hoyeau N, Henno S, Darragh TM, Alberts CJ, Clifford GM, Etienney I; ANRS-EP57-APACHES Study group. J Infect Dis. 2024
2. Incidence and Clearance of Anal Human Papillomavirus (HPV)-16 and HPV-18 Infection, and Their Determinants, Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men in France.Alberts CJ, Heard I, Canestri A, Marchand L, Fléjou JF, Piroth L, Ferry T, Didelot JM, Siproudhis L, Henno S, Poizot-Martin I, Darragh TM, Clifford GM, Combes JD, Etienney I; ANRS EP57 APACHES Study group.J Infect Dis. 2020
3. Determinants of high-grade anal intraepithelial lesions in HIV-positive MSM. Clifford GM, Siproudhis L, Piroth L, Poizot-Martin I, Radenne S, Reynes J, Lesage A, Heard I, Henno S, Fléjou JF, Marchand L, Combes JD, Etienney I; ANRS EP57 APACHES Study group. AIDS. 2018

4. Prevalence and Risk Factors for Anal Human Papillomavirus Infection in Human Immunodeficiency Virus-Positive Men Who Have Sex with Men. Combes JD, Heard I, Poizot-Martin I, Canestri A, Lion A, Piroth L, Didelot JM, Ferry T, Patey O, Marchand L, Flejou JF, Clifford GM, Etienney I; ANRS EP57 APACHES Study group. J Infect Dis. 2018

Preliminary Findings from 5-year follow-up of anal HSIL:

5) PERSISTENCE AND CLEARANCE OF HISTOLOGICAL ANAL HIGH-GRADE LESIONS IN MEN WHO HAVE SEX WITH MEN LIVING WITH HIV. Clifford GM et al. Abstract. International Papillomavirus Conference. Edinburgh. 2024. (to be submitted for full publication)

Contribution of baseline data to larger pooled analyses :

6)Incidence and Clearance of Anal Human Papillomavirus Infection in 16 164 Individuals, According to Human Immunodeficiency Virus Status, Sex, and Male Sexuality: An International Pooled Analysis of 34 Longitudinal Studies. Wei F, et al. Clin Infect Dis. 2023

7)Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Wei F et al Lancet HIV. 2021

8)A systematic review and meta-analysis of cytology and HPV-related biomarkers for anal cancer screening among different risk groups. Clarke MA, Int J Cancer. 2022

B - Secondary reuse of data and samples

This section concerns participants who have been included in the research and have consented to the re-use of their data and/or samples. Via its website and the present document, the research sponsor informs you of projects related to the secondary re-use of your data and/or samples.

B1. For the ongoing projects listed below, it is not possible to object to them, insofar as their deletion might make it impossible or compromise the achievement of the research objectives.

Projects in progress

Project title	APACHES Methylation
Project summary	Evaluation of host methylation markers as determinants of high-grade lesion and their evolution risk as a sub-study nested in the APACHES study samples. (this work was already approved in the original APACHES protocol, but with the necessity to obtain co-funding – this funding has since been obtained by a separate ANRS grant "APACHES Methylation".
Project start dates	January 2022

Project completion date	December 2025
Data recipients in France	Centre International de Recherche sur le Cancer, Lyon, France
Data recipient abroad	Amsterdam University (Anonymous sample ID numbers only).
Identity and data controller	Dr Gary Clifford, International Agency for Research on Cancer
Data and/or sample transfer	Samples transferred to Amsterdam University, Amsterdam for testing host methylation markers.
Data and/or sample retention period for this project *(from project start date)*	At CMG until December 2041.
Data category	Health data