Use of Systemic Therapies for the Treatment of Psoriasis in People Living with Controlled HIV: Inference-based Guidance from a Multidisciplinary Expert Panel

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Supplementary Material S1 – Methodology, Search Strategy, and Search Results

Detailed Methodology

Clinical Questions: At project initiation, authors drafted a project outline. Conference calls in November 2020 produced agreement on questions to be addressed and their priority. It was evident that the primary question did not have sufficient data to make confident determinations of real risk. Therefore, authors followed a logical process of dissecting concerns into component questions interrogating immune response. Systemic therapies for psoriasis block certain immune or metabolic pathways in an effort to normalize the aberrant immune actions manifesting as psoriasis. Immune blockade results in disease control but in parallel raises safety concerns. These concerns reflect our understanding of immune mechanisms relating to risk of infection, risk of malignancy, and possible off-target effects in PLHIV. Clinical trials evaluating therapies for psoriasis are tested in the non-HIV population. Clinical trials estimate rates for common, drug-related adverse events and benefits. We anticipate that any differences in response in PLHIV compared to the non-HIV population reflect differences in the immunological status between the two populations. Normalization of immune response is sufficient to conclude that benefits and risks of an intervention are highly similar to those experienced by the general, non-HIV population. The primary clinical question was anatomized in a layered, inference-based approach with successive layers denominated as: molecular level, atomic level, and sub-atomic level. Lower-level questions addressed aspects of a successively higher question (Supplementary Figure 1, main manuscript Table 1). Our objective was to identify data assessing immune response in controlled HIV patients, including residual immune alteration, and thereby identify the potential for altered risk or efficacy when treating psoriasis. Note that atomic section numbers (1.1.1 to 1.1.7) were re-ordered in the final manuscript, and some of the labelling in appendices S2 and S3 may reflect previous order.

Literature searches: The authors were divided into five working groups based on expertise and interest, to address the seven atomic questions identified by the entire group.

Structured scoping or systematic literature searches were performed for each atomic question between January 3rd-18th, 2021. We performed two systematic searches for 'HIV AND psoriasis', and 'HIV AND systemic psoriasis treatments' and assigned search results to atomic questions 1-7 (search terms and output below). Scoping searches in PubMed and Google Scholar focused on reviews and key articles for topics related to HIV (e.g., transplant, life expectancy, etc.) and guidance provided by HIV experts. Working group authors reviewed the list of articles, pre-filtered by medical writers to minimize redundancy. Members of each working group included articles based on relevance to the question and quality of the study (for detailed search strategy, see pages 5-7 of this appendix). As the evidence reviewed indirectly addresses the primary question, study selection was flexible in order to facilitate the inclusion of appropriate but indirect studies addressing immune reconstitution in PHLIV-s.

Data summaries, rating evidence and inferred level of support: After reviewing the filtered articles for their respective section, each author provided a summary of sub-atomic considerations from key articles, adding additional supporting references where they deemed necessary. Data summaries (Supplementary Material S2) were reviewed, discussed, and revised by all working group authors at five working group meetings that took place between May 12th and June 4th, 2021. Clinical questions were refined throughout the process to align with intent and available evidence. All of the final articles were ranked by level of evidence using a colour-coded schema based on modified Oxford Evidence Levels.[1] After reviewing the cumulative evidence as support for inference-based conclusions, working group authors provided a level of support for each sub-atomic consideration on a scale of 0-100, based on verbal transformations of subjective probability.[3] Support probability is an established method used in expert elicitation[3]. Support was defined as the degree to which the data provides logical credibility to the higher-level inference-derived statement. A level of support for overarching statements was derived using a mathematical model as a heuristic for logical inference which was then adjusted up or down according to the authors. One author (K.A.P.) worked with

deidentified data and fit the model. The logic-model was derived from de Morgan's law[4]. To better reflect the low level of evidence, the de Morgan model was heavily penalized with the result intended as a guide for the amalgamation of evidence (Supplementary Material S2). Authors reviewed the resulting level of support for higher statements and individually adjusted the calculated estimates via surveys. Final author meetings reviewed the process and final inference-based conclusions on July 26th and August 9th, 2021. The inference-based conclusions and caveats were finalized by the group during these meetings. All authors had opportunities to review summarized data (Supplementary Material S2) prior to the meetings. Authors adjusted or accepted the calculated level of support via anonymous surveys for atomic, molecular, and overarching guidelines conclusions.

Review and Implementation: An external review was conducted by supporting provincial organizations in Canada to gather feedback on the guidelines manuscript and obtain endorsement for support in dissemination of the guidelines. Similarly, patient organizations were invited to review the manuscript. Although a broad needs assessment survey was administered through the Canadian Association of Psoriasis Patients to seek the views of psoriasis patients who have HIV, none of the respondents reported having HIV. An annual needs assessment is planned, and this guideline will be updated when deemed necessary by the New Psoriasis Guidelines (NPG) committee. Clinical questions will be re-visited on an as-needed basis, taking into consideration available patient perspectives.

Methodology Limitations: Since we reviewed indirect evidence, there are significant gaps in knowledge and most of the data are extrapolated from the general population. The authors have made the best recommendations with these limited, indirect data. It is not possible to directly link the conclusions made to a specific justification, rather the sum of all the indirect evidence is used as support for each individual conclusion. Since most evidence reviewed was indirect evidence, it was complicated to utilize guideline tools such as GRADE[92] to assess methodologic limitations per study and consistency of results across studies of different designs

that looked at different outcomes. As such, risk of bias was not part of our analysis.

Instead of a Likert scale used in typical Delphi exercises, we used a scale of subjective probabilities used in expert elicitation (Figure S2) that is novel to clinical medicine. The variations of this scale are subtle, especially at the high and low ends. The unique mathematical aggregation of working group ratings for lower-level sub-atomic statements allowed for only panel members who reviewed and summarized the data to provide their ratings, while the whole panel was given a chance to anonymously accept or adjust the resultant level of support for all upper-level statements. Although this may be seen as a limitation since only 4 members rated the lower-level sub-atomic statements, we consider it a strength that only those panel members who reviewed the data in detail were required to rate it. All authors were asked to review the summaries and could adjust the ratings at their discretion. The mathematical aggregation assumes that each sub-question or body of evidence explored is largely independent of one another, which is not entirely the case. Despite these limitations, the aggregation approach allows inference-based conclusions to be re-constructed in a systematic way and helps guide decision making and inductive reasoning. Other approaches to aggregate the data are possible.

Guidelines Group Membership and Roles: All authors participated in reviewing the project outline and formation of clinical questions, reviewing literature search results for their respective working group(s) (as indicated below) and providing a summary for their assigned section. All authors participated in all rounds of voting and manuscript review/revision.

Kim. A. Papp, Dermatologist. Probity Medical Research Inc., Waterloo, ON, Canada. NPG Steering Committee Member and Guideline Chair. Oversaw all working groups and all aspects of guideline development, and participated in working group #1 (topic, life expectancy) and working group #4 (topic, immune assays and vaccine response). Constructed the mathematical model and conducted all analyses of anonymized data with the support of medical writers.

Jennifer. Beecker, Dermatologist. Division of Dermatology, The Ottawa Hospital, Ottawa, ON, Canada. NPG General Committee Member. Participated in working group #3 (topic, malignancies).

Curtis Cooper, Infectious Disease Specialist. University of Ottawa, Ottawa, ON, Canada

NPG Special Committee Member. Participated in working group #4 (topic, immune assays and vaccine response).

Mark G. Kirchhof, Dermatologist. Division of Dermatology, The Ottawa Hospital, Ottawa, ON, Canada NPG Steering Committee Member. Participated in working group #4 (topic, immune assays and vaccine response) and #5 (topic, transplant).

Anton L. Pozniak, HIV specialist. Chelsea and Westminster Hospital NHS Foundation Trust, London, UK. NPG Special Committee Member. Participated in working group #5 (topic, transplant).

Juergen K. Rockstroh, HIV specialist. Department of Medicine, University of Bonn, Bonn, Germany. NPG Special Committee Member. Participated in working group #2 (topic, infections).

Jan P. Dutz, Dermatologist. Skin Care Center, Vancouver, BC, Canada. NPG General Committee Member. Participated in working group #3 (topic, malignancies).

Melinda J. Gooderham, Dermatologist. SKiN Centre for Dermatology, Peterborough, ON, Canada. NPG Steering Committee Member. Participated in working group #5 (topic, transplant).

Robert Gniadecki, Dermatologist. Division of Dermatology, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada. NPG General Committee Member. Participated in working group #2 (topic, infections) and #3 (topic, malignancies).

Chih-ho Hong, Dermatologist. Dr. Chih-ho Hong Medical Inc., Surrey, BC, Canada. NPG General Committee Member. Participated in working group #3 (topic, malignancies).

Charles W. Lynde, Dermatologist. Lynde Institute for Dermatology, Markham, ON, Canada. NPG Steering Committee Member. Participated in working group #2 (topic, infections).

Catherine Maari, Dermatologist. Innovaderm Research Inc, Montreal, Quebec, Canada NPG General Committee Member. Participated in working group #2 (topic, infections).

Yves Poulin, Dermatologist. Centre de Recherche Dermatologique du Québec Métropolitain, Québec, QC, Canada. Former NPG Steering Committee Member. Participated in working group #1 (topic, psoriasis manifestations).

Ronald B. Vender, Dermatologist. Dermatrials Research Inc., Hamilton, ON, Canada. NPG General Committee Member. Participated in working group #1 (topic, psoriasis manifestations).

Sharon L. Walmsley, HIV specialist. Toronto General Hospital Research Institute, Toronto, ON, Canada. NPG Special Committee Member. Senior author provided feedback and guidance on content outline throughout the guidelines process. Participated in working group #1 (topic, life expectancy) and #3 (topic, malignancies).

Figure S1: Inference-based breakdown of questions. When the primary question is not directly addressable by clinical studies, questions are broken down into molecular level questions addressable by indirect data, atomic level questions and further into sub-atomic level considerations.

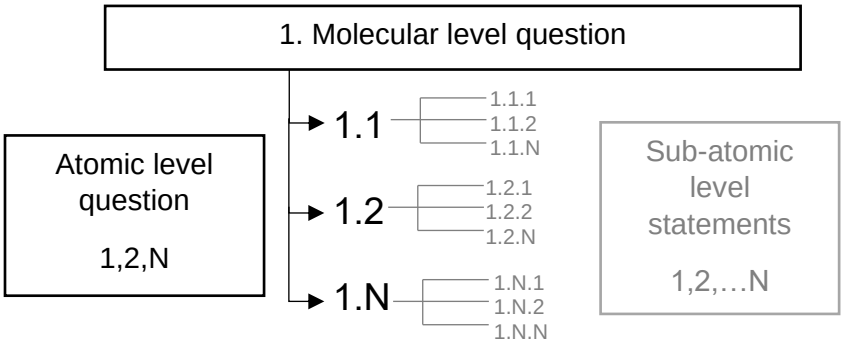
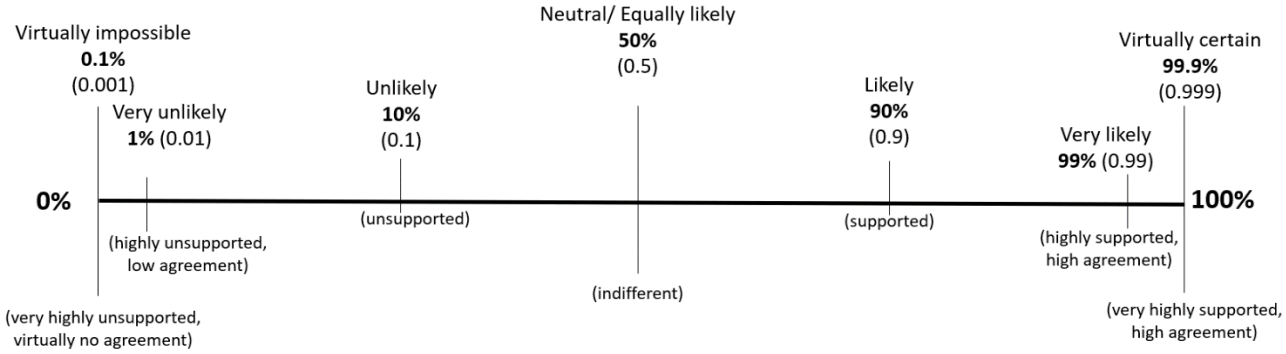


Figure S2: Scale for rating level of support. Support was ranked on a scale of 0-100, based on verbal transformations of subjective probability (Vick 2002).



Detailed Literature Search Strategy

Overall Search Parameters:

Language: English only
Exclude: children/adolescents/infants/neonates/maternal transfer

Most searches related to the **general HIV population were scoping reviews** (non-systematic) using PubMed and Google Scholar to identify key articles of interest. Results were filtered by keywords and reference lists of key review articles were checked to identify additional articles of interest. Scoping searches were conducted for the following questions/topics: 1.1.5.1 (infection in general/non-psoriasis HIV population), 1.1.6.1 (malignancy in general/non-psoriasis HIV population), 1.1.1 (functional assays), 1.1.2 (vaccine response).

Searches related to **psoriasis and HIV** and **HIV and psoriasis drugs/drug classes** were **systematic PubMed searches**. These searches were relevant to multiple clinical questions, and results were filtered using keywords to assign articles to the appropriate question.

Filtering Systematic Search Results and Inclusion/Exclusion: Search results were filtered for relevance by medical writers based on title and abstract (include/exclude/consider for author review). Reasons for exclusion were noted by medical writers (mainly non-relevant studies, non-HIV populations and laboratory studies). Medical writers generated a list of search results for each clinical question, filtered by keywords (type of study, drug, etc.). Working group authors reviewed and confirmed included/excluded articles. Articles were included for consideration if 75% of authors agreed on inclusion. Authors could add additional articles for consideration at their discretion. Relevant articles were summarized, evaluated, and discussed within the working groups, with the support of medical writers. Authors selected the best quality articles for inclusion in the data summary and discussion at working group meeting.

Note that atomic section numbers (1.1.1 to 1.1.7) were re-ordered in the final manuscript, and some of the labelling in the appendices may reflect previous numbering.

Search 1: Question 1.1.3 HIV morbidity/mortality
PubMed, publication dates 01 January 2016 to Present
Search date: 03 Jan 2021
Description: This search focused on higher-level review articles and large/recent cohort studies as identified by authors.

No	Search terms/description	Results (No. of articles)
1	["HIV" OR "acquired immunodeficiency syndrome" OR "human immunodeficiency virus"] (Title only) AND ["life expectancy" OR "survival" OR "mortality" OR "death"] (Title only)	975
2	Search No 1 Filters: Meta-Analysis, Review, Systematic Review	56
3	Additional articles from reference lists of selected articles from #2, and added by authors	+60
	No 2 and No 3 included for author review	116
	Articles selected by authors from above searches based on relevancy to clinical question	38
	Final articles included in section	**16**

Search 2: Question 1.1.4 psoriasis manifestations in PLHIV-s patients
PubMed, publication dates were 01 January 2001 to Present (18 Jan 2021).
Search date: 18 Jan 2021
Description: This search focused on recent articled in the post-antiretroviral therapy era, with addition of some pre-antiretroviral therapy articles for contrast. The focus was manifestations of psoriasis in HIV patients.

No	Search terms	Results (No. of articles)
1	"HIV" OR "AIDS" OR "human immunodeficiency virus" OR "acquired immunodeficiency syndrome" (anywhere) AND psoria* (anywhere)	358*
2	Selected for author review by medical writer, all others excluded due to relevance	85
3	Articles selected by authors from above searches based on relevancy to clinical question	30
	Final articles included in section	**23**

* articles from this search were also added to search results for other questions, where relevant.

Search 3: Questions 1.1.5.2, 1.1.6.2 (Psoriasis treatments and HIV)
PubMed, publication dates were 01 January 2001 to Present (18 Jan 2021).
Search date: 18 Jan 2021
Description: This search included psoriasis drugs (including generics and biosimilars), and HIV search terms. Articles were filtered by medical writers based on relevancy to questions 1.1.5.2 or 1.1.6.2.
Note that searches related to 1.1.5.1 and 1.1.6.1 (HIV in general, non-psoriasis) were scoping searches and as such a detailed search strategy is not documented.

No	Search terms	Results (No. of articles)
1	(("HIV"[Title/Abstract] OR "acquired immunodeficiency syndrome"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract]) AND (Acitretin*[Title/Abstract] OR Neotigason*[Title/Abstract] OR Adalimumab*[Title/Abstract] OR Cyltezo*[Title/Abstract] OR Humira*[Title/Abstract] OR Amgevita*[Title/Abstract] OR Hulio*[Title/Abstract] OR Hyrimoz*[Title/Abstract] OR Idacio*[Title/Abstract] OR Imraldi*[Title/Abstract] OR Apremilast*[Title/Abstract] OR Otezla*[Title/Abstract] OR Brodalumab*[Title/Abstract] OR Kyntheum*[Title/Abstract] OR Siliq*[Title/Abstract] OR Certolizumab*[Title/Abstract] OR Cimzia*[Title/Abstract] OR Ciclosporin*[Title/Abstract] OR Aqua-stasis*[Title/Abstract] OR Aquastasis*[Title/Abstract] OR Cequa*[Title/Abstract] OR Cyclo-derm*[Title/Abstract] OR Cycloderm*[Title/Abstract] OR Gengraf*[Title/Abstract] OR Hydro-stasis[Title/Abstract] OR Hydrostasis*[Title/Abstract] OR Ikervis*[Title/Abstract] OR Neoral*[Title/Abstract] OR Restasis*[Title/Abstract] OR Sangcya*[Title/Abstract] OR Sandimmune*[Title/Abstract] OR Verkazia*[Title/Abstract] OR Cyclosporin*[Title/Abstract] OR Etanercept*[Title/Abstract] OR Benepali*[Title/Abstract] OR Brenzys*[Title/Abstract] OR Davictrel*[Title/Abstract] OR Enbrel*[Title/Abstract] OR Erelzi*[Title/Abstract] OR Eticovo*[Title/Abstract] OR Nepexto*[Title/Abstract] OR Tunex*[Title/Abstract] OR Guselkumab*[Title/Abstract] OR Tremfya*[Title/Abstract] OR Infliximab*[Title/Abstract] OR Avsola*[Title/Abstract] OR Flixabi*[Title/Abstract] OR Inflectra*[Title/Abstract] OR Omvyence*[Title/Abstract] OR Remicade*[Title/Abstract] OR Remsima*[Title/Abstract] OR Renflexis*[Title/Abstract] OR Zessly*[Title/Abstract] OR Ixekizumab*[Title/Abstract] OR Taltz*[Title/Abstract] OR Methotrexate*[Title/Abstract] OR Jylamvo*[Title/Abstract] OR Metoject*[Title/Abstract] OR Nordimet*[Title/Abstract] OR Otrexup*[Title/Abstract] OR Rasuvo*[Title/Abstract] OR RediTrex*[Title/Abstract] OR Rheumatrex*[Title/Abstract] OR Xatmep*[Title/Abstract] OR Abitrexate*[Title/Abstract] OR Alltrex*[Title/Abstract] OR Artrait*[Title/Abstract] OR Atrexel*[Title/Abstract] OR Bendatrexat*[Title/Abstract] OR Carditrex*[Title/Abstract] OR Dermotrex*[Title/Abstract] OR Ebetrex*[Title/Abstract] OR	686

	Emtexate*[Title/Abstract] OR Ledertrexate*[Title/Abstract] OR Maxtrex*[Title/Abstract] OR Meisusheng*[Title/Abstract] OR Mexate*[Title/Abstract] OR Trexan*[Title/Abstract] OR Zexate*[Title/Abstract] OR Risankizumab*[Title/Abstract] OR Skyrizi*[Title/Abstract] OR Secukinumab*[Title/Abstract] OR Cosentyx*[Title/Abstract] OR Tildrakizumab*[Title/Abstract] OR Ilumetri*[Title/Abstract] OR Ilumya*[Title/Abstract] OR Ustekinumab*[Title/Abstract] OR Stelara*[Title/Abstract])) AND (("2001"[Date - Publication] : "2021"[Date - Publication])	
2	("HIV"[Title/Abstract] OR "acquired immunodeficiency syndrome"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract]) AND ("TNF alpha inhibit*" OR "TNF-alpha inhibit*" OR "TNFα inhibit*" OR "TNF-α inhibit*" OR "IL-17 inhibit*" OR "IL17 inhibit*" OR "IL-17A inhibit*" OR "IL17A inhibit*" OR "IL-17-alpha inhibit*" OR "IL-17 alpha inhibit*" OR "IL-17-α inhibit*" OR "IL-17α inhibit*" OR "IL-23 (p19) inhibit*" OR "IL-23 p19 inhibit*" OR "IL23 p19 inhibit*" OR "IL-23 inhibit*" OR "IL23 inhibit*" OR "IL-12/23 inhibit*" OR "IL12/23 inhibit*" OR "IL-12/IL-23 inhibit*" OR "IL12/IL23 inhibit*" OR "interleukin inhibit*" OR "PDE4 inhibit*" OR "PDE-4 inhibit*" OR "phosphodiesterase 4 inhibit*" OR "phosphodiesterase-4 inhibit*" OR "JAK inhibit*" OR JAKi OR "calcineurin inhibitor")	114
3	#1 AND #2	783
4	1.1.3.2 Selected for author review by medical writer, all others excluded due to relevance	96
5	Added for author review from search 2 (HIV+psoriasis, above)	+12
	Articles selected by authors from No 4 & No 5 based on relevancy to clinical question	33
	Final articles included in section 1.1.5.2 ***(includes additional articles added by authors in inference-based process)***	**50**
6	1.1.4.2 Selected for author review by medical writer, all others excluded due to relevance	27
7	Added for author review from search 2 (HIV+psoriasis, above)	+3
	Articles selected by authors from No 6 & No 7 based on relevancy to clinical question	14
	Final articles included in section 1.1.6.2 ***(includes additional articles added by authors in inference-based process)***	**43**

Search 4: Questions 1.1.7 (HIV and Transplant)
PubMed, publication dates were 01 January 2001 to Present (03 Jan 2021).
Search date: 03 Jan 2021
HIV AND [transplant* or allograft*] - restricted by study type
Description: This search included transplants in HIV populations as an indirect indicator of immune function in PLHIV-s, focus was high-level books and review articles on the topic to identify general trends.

No	Search terms	Results (No. of articles)
1	((("HIV"[Title/Abstract] OR "acquired immunodeficiency syndrome"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract]) AND (transplant*[Title] OR allograft*[Title])) AND (("2001"[Date - Publication] : "2021"[Date - Publication]))) AND (English[Language]) Filter: Books and Documents, Meta-Analysis, Review, Systematic Review	254
2	selected for author review by medical writer, all others excluded	126
	Articles selected by authors from above searches based on relevancy to clinical question	94
	Final articles included in section 1.1.7	35

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