Quality of life of people living with HIV : Measurement, determinants and priorities for care : Conception, formative research, and the first year of inclusions in the QuAliV ancillary study of the ANRS CO3 Aquitaine cohort.

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Par | By

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Qualité de vie des personnes vivant avec le VIH : Mesure, déterminants et axes de prise en charge

Conception, recherches préliminaires et première année de mise en œuvre de la sous-étude QuAliV dans la cohorte ANRS CO3 Aquitaine

Quality of life of people living with HIV: Measurement, determinants and priorities for care

Conception, formative research, and the first year of inclusions in the QuAliV ancillary study of the ANRS CO3 Aquitaine cohort.

Sous la direction de | thesis advisors
Pr Fabrice Bonnet & Pr François Dabis

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Résumé

L'infection par le VIH est devenue une maladie chronique en France. Néanmoins, le VIH et l'inflammation associée, les effets de l'exposition aux antirétroviraux, la prévalence élevée de facteurs de risque modifiables pour les maladies liées à l'âge, les effets d'autres co-infections virales couplés à la vulnérabilité sociale et économique font de la qualité de vie des personnes vivant avec le VIH (PVVIH) une préoccupation constante. Les recommandations de prise en charge incitent à prendre en compte la santé des PVVIH telle que définie par l'Organisation Mondiale de la Santé. Nous avons cherché à relever ce défi en concevant un module relié au système d'information de la Cohorte ANRS CO3 Aquitaine qui facilite le recueil de données rapportées par les patients (y compris la qualité de vie) par le biais d'instruments validés. Le contenu (composé de questionnaires courts et validés) du système est basé sur les recommandations thérapeutiques. Les propriétés psychométriques, la méthode et le mode d'administration ainsi que la longueur des questionnaires ont été évalués et des instruments papier ont été adaptés au format numérique selon les recommandations de l'International Society for Pharmacoeconomics and Outcomes Research. Les tests d'utilisabilité du nouveau module du système d'information se sont déroulés en deux cycles (1er auprès des experts et 2ème auprès des PVVIH). Nous avons demandé aux participants d'accomplir une série de tâches en utilisant la méthode « penser à voix haute » et de répondre à l'échelle de « System Usability Scale » (SUS). Nous avons calculé un score synthétique et défini a priori le « succès » comme un score d'utilisabilité de 70. Au premier cycle, les experts ont rapporté des scores SUS moyens de 65 ± 18,87 et les patients, au deuxième cycle, des scores SUS moyens de 85 ± 5,4 (p=0,032). A ce jour, le recueil (électronique et papier) de données rapportées par les patients, y compris la qualité de vie liée à la santé, est en cours dans cinq hôpitaux de la région Nouvelle Aquitaine. Parmi ceux qui ont été invités à participer (juillet 2018-mai 2019), 90,5% (1 521/1 681) ont accepté, 7,1 % (119/1 681) ont refusé et 2,4 % (41/1 681) étaient non- éligibles. Parmi ceux qui ont accepté, 82% (1246/1 521) ont été considérés comme ayant satisfait aux exigences de base du nouveau système d'information tandis que 18 % (275/1 521) n'avaient pas d'adresse courriel personnelle. Les propriétés métriques de l'instrument de mesure choisi pour évaluer la qualité de vie (liée à la santé) dans notre population ont été ensuite évaluées sur un échantillon de 586 PVVIH, âgées de 56 ans en moyenne. 73 % étaient des hommes, 85 % étaient d'origine française, 99% étaient sous antirétroviraux et 93 % avaient une charge virale indétectable. La version française du WHOQOL-HIV BREF a des propriétés de mesure acceptables et sa conceptualisation large de la qualité de vie (au-delà de la santé physique et mentale) peut s'avérer particulièrement utile dans notre population. Sur une échelle de 4 à 20, le domaine des croyances personnelles avait le score moyen le plus élevé (15,04 ± 3,35) et le domaine de la santé psychologique le plus faible (13,70 ± 2,78). Les aspects (score de 1 à 5) les plus altérés étaient les relations personnelles (2,7 ± 1,25) et les ressources financières (2,9 ± 1,15). Les femmes ont obtenu des scores nettement inférieurs à ceux des hommes pour 12 sur 29 aspects, y compris les cinq aspects spécifiques au VIH. Les personnes nées en Afrique du Nord ou en Afrique subsaharienne ont des score plus faibles dans le domaine « environnement de vie » que celles nées en France (13,19 ± 2,10 contre 14,52 ± 2,56, p<0,001). Cette nouvelle démarche a été la première étape dans l'établissement d'un nouveau rapport avec les personnes prises en charge dans la région. Elle a permis de mettre en lumière des domaines qui, selon nous, doivent être particulièrement ciblés afin de développer avec succès de nouveaux modèles de soins et de services sociaux qui tiennent compte des besoins globaux des PVVIH et y répondent efficacement.

Mots clés : qualité de vie liée à la santé, données rapportées par les patients, maladies chroniques, e-santé, VIH

Abstract

HIV has become a chronic disease in France. Nevertheless, HIV and associated inflammation, the effects of antiretroviral exposure, the high prevalence of modifiable risk factors for age-related diseases (e.g. smoking) and the effects of other viral co-infections together with social and economic vulnerability make the quality of life of people living with HIV (PLWH) an ongoing concern. French clinical guidelines have urged providers to address PLWH's health as defined by the World Health Organisation. To take on this challenge, we designed an electronic module for the collection of patient-reported outcome linked the ANRS Aquitaine cohort's data capture and visualisation system. The proposed solution relies on validated questionnaires and its content is based on current clinical guidelines on HIV management. The questionnaires' psychometric properties, administration method/mode, and length were evaluated and paper-based instruments adapted following the International Society for Pharmacoeconomics and Outcomes Research's guidance. Two rounds of usability evaluations were conducted first in research staff and the PLWH. We asked participants to complete a set of tasks using the 'think aloud' method and respond to the System Usability Scale (SUS). Input from experts/investigators and subsequently patients was used to improve features of the system. We calculated a summary score and defined "success" a priori as a usability score of 70. Experts reported average SUS scores of 65 ± 18.87 and patients reported average SUS scores of 85 ± 5.4 (p=0.032). To date, the collection of (electronic and paper) patient-reported outcomes, including health-related quality of life, is underway in five hospitals. Of those invited to participate (July 2018-May 2019), 90.5% (1,521/1,681) accepted, 7.1% (119/1,681) refused and 2.4% (41/1,681) were not eligible. Of those who accepted, 82% (1,246/1,521) were considered to have met the basic requirements of the newly designed solution whereas 18% (275/1,521) did not have a personal email address and/or a reliable Internet connection and were provided an identical paper questionnaire. We verified the psychometric properties of the WHOQOL-HIV BREF instrument, chosen to assess (health-related) quality of life in our population in a sample of 586 PLWH (aged 56 on average, 73% were male, 85% were of French origin, 99% were treated and 93% had an undetectable viral load). The French version of the WHOQOL-HIV BREF has acceptable measurement properties and its broad conceptualization of quality of life, going beyond physical and mental health, may be particularly useful in our population. On a scale of 4 (worst) to 20 (best), the personal belief domain had the highest average score (15.04 ± 3.35) and the lowest psychological health domain (13.70 ± 2.78). The most impaired facets (score of 1-5) were personal relationships (2.7 ± 1.25) and financial resources (2.9 ± 1.15). Women scored significantly lower than men on 12 of 29 facets, including the five HIV-specific facets. People born in North Africa or sub-Saharan Africa have lower scores in the environmental health domain than those born in France (13.19 ± 2.10 versus 14.52 ± 2.56, p<0.001). This work has been the first step in fostering a new relationship with those in care in the region. It has resulted in highlighting a number of areas that we feel need to be addressed in order to successfully develop new value-based models of care and social services which take into consideration and efficiently respond to PLWH's global needs.

Key words: health-related quality of life, patient-reported outcomes, chronic diseases, e-health, HIV

Executive Summary in French | Résumé substantiel en français

Au cours de la dernière décennie, plusieurs innovations biomédicales ont radicalement changé notre façon d'appréhender la prévention et le traitement de l'infection par le VIH, en particulier les tests d'orientation rapide de dépistage, les auto-tests, le traitement universel (approche dite TasP), la prophylaxie pré-exposition (PrEP), [1, 2]. Ainsi, il est recommandé depuis 2013 d'initier un traitement antirétroviral (TARV) chez toutes les personnes séropositives quelque soient leurs taux de CD4 [3]. L'impact positif des TARV sur la santé globale des patients mais aussi sur la réduction du risque de transmission du virus aux partenaires n'est plus à démontrer [4, 5]. Les molécules désormais disponibles en France sont plus efficaces, comportent moins d'effets secondaires, et ont une formulation simplifiée permettant une très bonne observance. Tous ces éléments font que les PVVIH peuvent prétendre à une espérance de vie proche à celle de la population générale en étant à l'abri des infections opportunistes liées à l'immunodéficience [6]. L'infection par le VIH est devenue une maladie chronique en France puisque, 96% des PVVIH prises en charge sont sous TARV et 94% des personnes traitées depuis au moins 6 mois ont une charge virale indétectable [7]. Néanmoins, le VIH et l'inflammation associée, les effets de l'exposition aux antirétroviraux, la prévalence élevée de facteurs de risque modifiables pour les maladies liées à l'âge (ex. le tabagisme), les effets d'autres co-infections virales couplés à la vulnérabilité économique et sociale font de la qualité de vie des PVVIH une préoccupation constante [8].

Les recommandations du groupe d'experts français de prise en charge de l'infection par le VIH incitaient dès leur rapport de 2013 à rendre la vie des PVVIH « la plus harmonieuse possible tant sur le plan physique que psychique et sociale, permettant au plus grand nombre (...) de vivre dans un état de bonne santé au sens OMS du terme » [4]. Nous avons cherché à relever ce défi, en concevant un système d'information qui nous permettra à terme de mesurer la capacité des prestataires de soins à atteindre cet objectif si noble. Il a été donc important de choisir un (des) indicateur(s) du bon état de santé tel qu'il est défini par l'Organisation Mondiale de la Santé (OMS) et s'assurer que ceux-ci sont bien adapté aux besoins des PVVIH. La notion de la qualité de vie émerge d'un cadre théorique basé sur la définition holistique de l'état de santé de l'OMS. Il s'agit de « la perception qu'a l'individu de sa place dans l'existence, dans le contexte de la culture et du système de valeurs dans lesquels il vit, en relation avec ses objectifs, ses attentes, ses normes et ses inquiétudes » [4]. Lorsqu'on cherche à estimer à quel point une maladie donnée affecte la vie d'un patient, le terme « qualité de vie liée à la santé (QVLS) » est employé.

Le choix de la QVLS comme critère de jugement est bien établi dans le champ de la recherche clinique. La QVLS est considérée comme une donnée rapportée par le patient, souvent par le biais d'un auto-questionnaire. Les données rapportées par les patients sur leur fonctionnement et leur bien-être font de plus en plus l'objet d'un recueil standardisé en soin courant. Pendant plusieurs décennies, malgré l'apport potentiel de ces informations, le recueil de données rapportée par les patients **en soins courants** a été freiné par les barrières d'ordre logistique, méthodologique et idéologique. Les services manquaient des moyens pour recueillir et analyser ces données. Les soignants ont été également sceptiques sur les propriétés métriques des instruments de mesure ainsi que l'utilité du recueil standardisé. Le progrès au niveau des technologies de l'information et de la communication a allégé le travail associé, potentiellement facilitant l'intégration des données rapportées par les patients pour la recherche (en soins courants) et la prise en charge.

A ce jour, à notre connaissance, la grande majorité d'exemples d'intégration des données rapportées par les patients en soins courant vient des Etats-Unis. La cohorte de personnes séropositives de l'Université de Washington a été parmi les premières à expérimenter la collecte informatisée et systématique des données rapportées par les patients. Crane et coll. ont décrit les efforts entrepris pour mettre en place la collecte systématique de données rapportées par les patients par voie électronique dans la prise en charge du VIH, concluant qu'elle était à la fois prometteuse pour la recherche et les soins [9]. Les défis associés au recueil de données de bonne qualité dans les soins courants et les limites des données enregistrées dans les dossiers médicaux, informatisés ou non, des patients ont pu être remarqué par Kozak et coll. [10]. Les exigences des soins et la volonté des patients de ne pas divulguer des informations sensibles peuvent compromettre l'exhaustivité et la qualité des données saisies dans les dossiers médicaux. Dans une étude de 2012, menée à la clinique VIH/Sida de l'Université de l'Alabama à Birmingham, des chercheurs ont comparé les données auto-déclarées et les données enregistrées dans le dossier médical informatisé et ont regardé l'association entre l'abus de substances, la dépression et la faible observance des TARV chez les PVVIH. Non seulement les auteurs ont documenté des différences significatives dans la prévalence de la consommation d'alcool et d'autres drogues et de la dépression auto-déclarées par rapport à celles documentées dans le dossier médical, mais ils ont aussi constaté que les mesures auto-déclarées (plutôt que celles documentées dans le dossier) étaient mieux corrélées avec une observance moins bonne des traitements antirétroviraux [10]. Cette recherche suggère que la collecte des données rapportées par les patients est un moyen potentiellement plus fiable de capter des données dans

des domaines sensibles comme la santé sexuelle, la consommation d'alcool et d'autres drogues et certains ressentis.

Ce projet a été conduit au sein de la cohorte ANRS CO3 Aquitaine. Celle-ci a été mise en place en 1987 à partir d'un système de surveillance épidémiologique et clinique de l'infection par le VIH en région qui avait pour objectif général de recueillir de manière standardisée des informations cliniques, biologiques, thérapeutiques et épidémiologiques concernant les sujets séropositifs suivis dans cinq services de médecine interne et de maladies infectieuse du Centre Hospitalier Universitaire (CHU) de Bordeaux. Sa mise en place dès 1987 et son extension progressive à tous les hôpitaux publics en région a permis d'une part de mieux caractériser la population des PVVIH prises en charge en Aquitaine et d'autre part d'aborder de nombreuses problématiques liées à l'histoire naturelle de l'infection puis à ses traitements. Ses objectifs ont donc évolué avec le développement des connaissances tant dans le domaine de l'infection elle-même que de sa prise en charge. Aujourd'hui, l'objectif principal est d'étudier les tendances temporelles de l'infection sous traitement et de toutes ses conséquences en termes de comorbidités et de pronostic.

La cohorte ANRS CO3 inclut et suit des PVVIH dans 13 hôpitaux publics, tous localisés en ex-Aquitaine : Agen, Arcachon, Bayonne, Bordeaux (5 centres), Dax, Libourne, Mont-de-Marsan, Orthez, Pau, Périgueux et Villeneuve sur Lot. Depuis 2013, les données médicales relevant de la prise en charge courante des PVVIH et recueillies dans le cadre de la cohorte sont toutes systématiquement saisies sur un eCRF en ligne sur le logiciel ARPEGE® par les TEC/ARC dans les différents centres participants et un programme permet le transfert des données des examens biologiques entre le CHU de Bordeaux et la base de données de la cohorte. ARPEGE (1.0) est un logiciel développé dans Microsoft ASP.NET, une plateforme open-source pour le développement informatique, accessible sur un site internet sécurisé et dont les données sont stockées dans un système de gestion de base de données (SGBD) appelé Microsoft SQL Server 2014. Le logiciel ARPEGE 1.0 a été conçu pour faciliter le recueil de données dans le cadre de la recherche et permettre l'affichage de plusieurs modules : eCRF, états récapitulatifs des données d'un patient par thématique (VIH, hépatites, métabolique, « rénal, osseux et urinaire », « sérologies CMV toxo syphillis »), synthèse, module de requête sur les données. Ces modules sont destinés aux ARC, TEC, MEC, infirmiers et aux cliniciens. Comme avec d'autres systèmes d'information conçu pour la recherche, il ne disposait pas d'accès dédié aux patients. La première étape de ce projet était donc de développer un accès dédié aux PVVIH elles-mêmes afin qu'elles puissent fournir des informations sur leur état de santé subjectif.

Pour ce faire, le protocole de la cohorte ANRS CO3 Aquitaine a dû être amendé afin d'intégrer la sous-étude que nous avons nommé QuAliV. Il a été soumis avec l'ensemble des documents relatifs à l'étude (le contenu du site Internet, les brochures d'information, l'affiche, et le questionnaire) par son promoteur, le Centre Hospitalier de Bordeaux, à toutes les instances réglementaires et a obtenu toutes les autorisations nécessaires au lancement du projet, notamment celles concernant la sécurité et la confidentialité de toutes les données recueillies. Ainsi, le projet a été soumis au Comité de Protection des Personnes Sud-Ouest et Outre-Mer III qui a donné un avis favorable le 18 septembre 2017 et le 2 mai 2018 et puis à la Commission nationale de l'informatique et des libertés (CNIL) qui a donné un avis favorable le 18 mars 2018. En parallèle, nous avons conçu et mis à disposition un nouveau site Internet, spécifique à l'étude : www.qualiv.fr, expliquant les objectifs et l'intérêt de cette étude pour la prise en charge du VIH dans l'ère actuelle de la prise en charge. C'est à partir de cette page qu'on peut se connecter à son compte personnel et participer à l'étude, muni de son numéro « QuAliV ». Sur le logiciel ARPEGE®, une nouvelle interface de création de compte et de connexion a été développée pour permettre à des utilisateurs non professionnels de créer un compte et de se connecter en toute sécurité. Un remodelage de la gestion des utilisateurs et de la partie administration a dû être fait pour prendre en compte ces nouveaux profils utilisateurs. Pour s'adapter à tous les types d'utilisateurs, l'interface développée est "responsive" pour offrir une consultation et une utilisation confortable sur différentes tailles d'écrans : ordinateur de bureau, tablette et smartphone. D'autre part, pour simplifier la gestion du suivi de la non-opposition des participants à l'étude, nous avons mis en place pour la première fois au CHU de Bordeaux, la gestion d'une version électronique à la création du compte d'une note de non opposition réglementaire. La création des auto-questionnaires avec l'ajout d'une vidéo d'introduction, d'un état d'avancement de la complétude des questionnaires a permis des retours positifs de patients lors d'une phase test préalable au démarrage de l'étude. Un programme de relance automatique par mail a été rapidement élaboré et mis en place pour les participants qui n'ont pas complétés plus de 70% de leurs questionnaires.

Comme décrit dans le protocole de recherche que nous avons publié dans la revue à comité de lecture « Journal of Medical Internet Research » [11], la principale caractéristique de l'interface est la fonction d'enquête en raison de l'imbrication de la solution dans une étude de cohorte hospitalière de longue date. La première caractéristique est de faciliter la collecte de données sur la qualité de vie et d'autres données rapportées par les patients par le biais d'instruments validés. Le contenu du système de collecte de données rapportées par les patients est basé sur

les recommandations thérapeutiques pour les personnes traitées pour le VIH et les comorbidités associées [4]. Les recommandations françaises prévoient un bilan de santé annuel, au cours duquel un certain nombre de questions devraient être abordées par le médecin spécialiste du VIH en fonction de l'âge et du sexe des patients. Selon la taxonomie des applications des données rapportées par les patients en pratique clinique, établie par Greenhalgh, le système proposé vise à optimiser ce bilan en demandant au patient de remplir un questionnaire standardisé avant sa visite. Le système d'information vise à évaluer la privation sociale et matérielle de l'individu [12], la qualité de vie multidimensionnelle (WHOQOL-HIV BREF) [13], la charge de traitement (Treatment Burden Questionnaire) [14], l'activité physique (la version abrégée du questionnaire international sur l'activité physique), la consommation d'alcool et le dépistage des comportements de consommation à risque (AUDIT-C, FACE) [15], la consommation de tabac et de nicotine et le dépistage de la dépendance au tabac (Fagerström), au cannabis (CAST) et à la drogue, enfin la dépression (PHQ-9) [16]. Il permet également aux patients de signaler d'autres problèmes liés au traitement dans un champ de texte libre. Le cas échéant, nous avons suivi les recommandations formulées par l'International Society for Pharmacoeconomics and Outcomes Research ePRO Task Force sur l'adaptation des instruments papier afin de garantir que les données produites soient équivalentes ou supérieures à celles produites par les méthodes d'administration sur papier [17].

Avant de pouvoir lancer ce nouveau module du système d'information, il a été indispensable d'évaluer son ergonomie. **Le deuxième chapitre** de cette thèse témoigne de ce processus. Les résultats de cette étape de recherche ont été publiés dans la revue Journal of Medical Internet Research Formative Research. Nous avons privilégié des méthodes empiriques [18]. Les tests d'utilisabilité du système se sont déroulés en deux phases. Nous avons ainsi mené la première phase au sein de notre institut de recherche auprès de collègues qui connaissaient bien le projet, mais qui n'étaient pas très impliqués dans son développement. Une fois les problèmes identifiés au cours de cette première phase résolus, nous avons effectué un deuxième cycle de tests d'utilisabilité sur un échantillon de personnes vivant avec le VIH. Nous avons demandé aux participants d'accomplir une série de tâches en utilisant la méthode « penser à voix haute » et de répondre à l'échelle de « System Usability Scale » (SUS). Nous avons calculé un score synthétique et défini a priori le « succès » comme un score d'utilisabilité de 70.

Les caractéristiques de conception proposées ont été bien accueillies par les évaluateurs au cours des deux cycles des tests utilisateurs. Les utilisateurs ont trouvé claires et utiles les informations fournies dans la brochure et sur le site Internet expliquant les objectifs de l'étude. Ils ont rapidement compris comment le numéro personnalisé spécifique à l'étude serait utilisé

pour créer leur compte et lier leurs données cliniques et biologiques déjà enregistrées dans l'étude de cohorte. Nous avons été en mesure d'identifier un certain nombre de difficultés au cours de la première phase des tests d'utilisabilité et d'apporter des solutions. Au premier cycle, les experts ont rapporté des scores SUS moyens de 65 ± 18,87 et les patients, au deuxième cycle, des scores SUS moyens de 85 ± 5,4 (p=0,032).

Le principe du projet initial était de concevoir un système d'information pour permettre le recueil de données rapportées par les patients et de l'expérimenter à une échelle raisonnable pour pouvoir proposer à terme son utilisation à grande échelle (l'ensemble de la cohorte régionale et développement possible pour la population servie par le COREVIH de la Nouvelle Aquitaine à partir de 2017). A ce jour, l'étude est en cours dans cinq services sur les trois sites du CHU de Bordeaux (St André, Pellegrin, Haut Lévêque), au Centre Hospitalier du Côte Basque et au Centre Hospitalier de Périgueux. **Le troisième chapitre de la thèse** résume les résultats concernant l'acceptabilité de la démarche telle que proposée pendant cette phase initiale de recherche. J'y résume le recrutement entre la date de l'ouverture du premier centre, le 23 juillet 2018 et le 15 mai 2019 et présente les indicateurs définis à priori pour évaluer l'acceptabilité initiale. Au total, 1 752 participants théoriquement éligibles ont été vus pendant la période d'étude (23 juillet 2018 - 15 mai 2019). Vingt observations ont été exclues en raison de retards dans la saisie des données ou de l'absence de suivi. Parmi ceux qui étaient théoriquement éligibles, 97,1 % (1 681/1 732) ont reçu de l'information et ont été invités à participer à l'étude. Cinquante et un n'ont pas été invités à participer soit parce que l'investigateurs les a jugés non-éligibles (n=32) ou parce qu'ils ont refusé catégoriquement (n=19). Parmi ceux qui ont été invités à participer, 90,5% (1 521/1 681) ont accepté, 7,1 % (119/1 681) ont refusé et 2,4 % (41/1 681) étaient non- éligibles. Parmi ceux qui ont accepté, 82 % (1 246/1 521) ont été considérés comme ayant satisfait aux exigences de base du module ePROS, tandis que 18 % (275/1 521) n'avaient pas d'adresse courriel personnelle et/ou de connexion Internet fiable. Un questionnaire papier a été par conséquent remis à 273 participants. Nous avons pu conclure que le circuit papier de l'étude était donc important à maintenir. Certains participants qui satisfaisaient aux exigences de base du module ePROs ont par la suite demandé un questionnaire papier (n=25). Parmi ceux qui ont accepté et satisfait aux exigences de base du module ePROs, 37,4 % (466/1 246) étaient inscrits au 4 juin 2019. Parmi les 466 qui ont créé leur compte, 65,5% (305/466) l'ont fait dans la semaine suivant la consultation et 88,2 % (411/466) dans le mois suivant. Parmi ceux qui ont créé leur compte, 425 ont soumis leur questionnaire et 362 l'ont fait dans le mois suivant sa création. La complétude des questionnaires est très bonne parmi ceux qui entament la création de compte.

Parmi ceux qui avaient reçu un questionnaire papier, 68,9 % (188/273) l'avaient retourné avant le 4 juin 2019 et 66,3 % (181/273) de ceux qui l'avaient retourné étaient suffisamment complets et lisibles pour être saisis.

Comme on pouvait s'y attendre, ceux qui répondaient aux exigences de base du module ePRO et qui ont rempli les questionnaires par rapport à ceux qui ont rempli un questionnaire papier étaient très différents. Ceux qui ne remplissaient pas les conditions de base requises pour le module ePROs étaient le plus souvent des personnes âgées, des femmes et des personnes d'origine africaine. Ils avaient plus souvent contracté le VIH par voie hétérosexuelle que par d'autres voies de transmission. Malgré ces différences, les groupes présentaient des caractéristiques cliniques similaires. 68,7 % de ceux qui ne satisfaisaient pas aux exigences de base du module ePROs avaient un nombre de cellules CD4 supérieur à 500 cellules/ml au cours des trois dernières années de la consultation, contre 71,5 % (p= 0,136). De même, 90,6 % de ceux qui ne satisfaisaient pas aux exigences de base présentaient une charge virale indétectable, comparativement à 91,5% (p = 0,066).

Enfin, le **quatrième et dernier chapitre** concerne les propriétés métriques de l'instrument de mesure choisi pour évaluer la qualité de vie (liée à la santé) dans notre population. Il s'agit d'une étape préalable à l'analyse de la qualité de vie et ses déterminants dans l'ère actuelle de la prise en charge. Cette analyse a été menée sur un échantillon de 586 participants ont été recrutés consécutivement à leurs consultations et ont rempli soit un questionnaire en ligne (n=406) soit un questionnaire papier auto-administré (n=180). Les moyens et les écart-types ont été calculés et la présence des effets plafond et plancher recherchée. La cohérence interne et la validité de structure ont été évaluées à l'aide i) des coefficients alpha de Cronbach par domaine et ii) une analyse factorielle de confirmation. Les validités concurrente, convergente et discriminante ont été évaluées avec les corrélations de Pearson et la validité « des groupes connus », selon les catégories définies par les seuils de cellules CD4, la charge virale et les stades de la maladie définis par le CDC. Les différences en termes de scores moyens des domaines selon le sexe, le pays d'origine et les groupes de transmission ont ensuite été évaluées.

Leur âge médian était de 56 ans, 73 % étaient des hommes, 85 % étaient d'origine française, 99% étaient sous antirétroviraux et 93 % avaient une charge virale indétéctable. Nous avons trouvé des effets de plancher pour un item et des effets de plafond pour 11 items. La cohérence

interne a été considérée comme acceptable (étendue α 0,63-0,79). L'analyse factorielle de confirmation a montré que la structure « originale » du WHOQOL-HIV BREF produit un ajustement acceptable (SRMR = 0.059; CFI= 0.834; RMSEA= 0.07; 90% CI: 0.06 - 0.08). Elle a également montré une bonne validité concurrente, convergente et divergente. Le domaine des croyances personnelles avait le score moyen le plus élevé (15,04 ± 3,35) et le domaine de la santé psychologique le plus faible (13,70 ± 2,78). Les aspects les plus altérés étaient les relations personnelles (2,7 ± 1,25) et les ressources financières (2,9 ± 1,15). Les femmes ont obtenu des scores nettement inférieurs à ceux des hommes pour 12 sur 29 facettes, y compris les cinq facettes spécifiques au VIH. On peut conclure que la version française du WHOQOL-HIV BREF a des propriétés de mesure acceptables. Sa conceptualisation large de la QVLS, qui va au-delà de la santé physique et mentale, peut s'avérer particulièrement utile dans notre population plus âgée, sous TARV depuis de nombreuses années et avec une charge virale contrôlée.

Je conclus en discutant des forces et les limites des decisions prises lors de la conception de cette démarche au sein d'une cohorte de PVVIH au vue des résultats préliminaires tirés en préparation de l'étude et sur les 10 premiers mois d'inclusions. Je mets ensuite ces résultats en perspective vis-à-vis les recherches et actions prévues.

Scientific production, grants, training and additional activities

Publications

Barger, D., *et al.* (2018). "Integrating Electronic Patient-Reported Outcome Measures into Routine HIV Care and the ANRS CO3 Aquitaine Cohort's Data Capture and Visualization System (QuAliV): Protocol for a Formative Research Study." JMIR Research Protocol.

Barger, D., *et al.* (2019). "Web-based module for the collection of electronic Patient-Reported Outcomes in people living with HIV in Nouvelle Aquitaine, France : Usability evaluation." JMIR Formative Research."

Barger, D., *et al.* "Assessing the psychometric properties of the French WHOQOL-HIV BREF within the ANRS CO3 Aquitaine Cohort's QuAliV Ancillary Study." Under consideration at Health and Quality of Life Outcomes.

Presentations

2020	Oral Presenter, Journée Scientifique Sidaction 2020 | Paris, France
2019	Poster Presenter, 17th European AIDS Clinical Society | Basel, Switzerland
2019	Invited Speaker, Société Française de Lutte Contre le SIDA | La Rochelle, France
2019	Invited Speaker, Journées Régionales du Sud-Ouest 2019 | Bordeaux, France
2019	Poster Presenter, International Workshop for Observational HIV Databases | Athens, Greece
2019	Poster Presenter, Journée Scientifique de Sidaction | Paris, France
2018	Poster Presenter, International Workshop for Observation HIV Databases | Fuengirola, Spain
2017	Invited Speaker, Setting-up and funding your PhD, Research Project Workshop, Network of young social science researchers sponsored by the ANRS | Paris, France
2017	Invited Speaker, Round table "Perspectives on Quality of Life in People living with HIV", COREVIH Aquitaine | Bordeaux, France
2017	Invited Speaker, Journées Régionales du Sud-Ouest 2017 | Bordeaux, France
2017	Poster Presenter, 11ème Conférence Francophone d'Epidémiologie Clinique (EPICLIN) | Saint-Etienne, France

Grants related to the subject of the thesis, training or teaching

- 36-month young researcher/investigator grant (bourse "Jeune chercheur") from the charity Sidaction to conduct doctoral research (2016 – 2019)
- Scholarship for European public health experts to attend the 17th European AIDS Conference, Basel Switzerland (2019)
- Training Mobility Grants, Ecole des Hautes Etudes en Santé Publique Doctoral Network (2017, 2018, 2019)
- Erasmus+ Teaching Mobility for Academic Staff, Universidad de Navarra (2018, 2019)
- Travel Grant, Ecole des Hautes Etudes en Santé Publique Doctoral Network (2019)
- Travel Grant, Ecole doctorale Sociétés, Politique, Santé Publique, Université de Bordeaux (2019)
- Travel Grant, Fédération de Recherche Santé Publique, Société (2018)

Additional activities

2016 -	Distance Learning Tutor, London School of Hygiene and Tropical Medicine
2017-19	Teaching Assistant - Monitor à l'initiation à l'enseignement supérieur, Université de Bordeaux
2018 -	Member, Digital Public Health Graduate Program, Université de Bordeaux
2016-19	Member, Doctoral Network, Ecole des Hautes Etudes en Santé Publique
2017 -	Member, Network of HIV/AIDS Young Social Science Researchers
2018	Organising Committee, Symposium: How are patient-reported outcomes transforming public health in France? | Paris, France
2018	Invited Webinar, What are patient-reported outcome measures and how are they used in drug development? European AIDS Treatment Group | Brussels, Belgium

Other publications (2016-2019)

Aïm-Eusébi A., Prothon E., Majerholc C., Martignon G., Albertini P., **Barger D**., Yazdanpanah Y, Aubert J. (2017) The acceptability and effectiveness of a questionnaire for the identification of risk factors for HIV and hepatitis B and C and guidance on its administration: An observational study in a general practice setting in Paris, France. European Journal of General Practice.

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Abbreviations

Acquired immunodeficiency syndrome: AIDS

Age-associated non-communicable co-morbidites: AANCC

Antiretroviral therapy: ART

Case Report Form: CFR

Clinical Research Associate: CRA

Electronic Case Report Form: eCRF

Food and Drug Administration: FDA

Health-related quality of life: HRQoL

Human Immunodeficiency Virus: HIV

Information and Communication Technologies: ITC

Men who have sex with men: MSM

Non-nucleoside reverse-transcriptase inhibitor: NNRTIs

Nucleoside reverse-transcriptase inhibitor: NRTIs

Patient-reported outcomes: PROs

People living with HIV: PLWH

Quality of Life: QoL

Randomised controlled trials: RCT

Triple combination antiretroviral therapy: cART

World Health Organisation: WHO

1. Introduction

1.1. Human immunodeficiency virus and its treatment then and now

Human immunodeficiency virus (HIV) is a *Lentivirus*, family Retroviridae [19]. Transmitted sexually, through blood or perinatally, the retrovirus integrates into the host genome of the infected cells. HIV infection mainly targets CD4 T lymphocytes (CD4 cells), progressively destroying them as it replicates, resulting in acquired immunodeficiency syndrome (AIDS). People with AIDS are susceptible to opportunistic infections and present with cancers caused by latent viruses [20].

Prior to 1996, HIV-infected individuals were treated with a nucleoside reverse-transcriptase inhibitor (NRTIs), available as of 1986-7, and later, as of 1995, with two NRTIs. Protease inhibitors, a new drug class, combined with two NRTIs, were shown to reduce levels of HIV RNA and increase CD4 T cell counts and improve prognosis [21]. Another class of drugs, non-nucleoside reverse-transcriptase inhibitor (NNRTIs), was also used in combination with NRTIs. The expanded use of this "triple combination antiretroviral therapy" or cART reduced opportunistic infections, the length of hospitalisation and mortality [22-24].

It was initially recommended that cART be started as soon as possible [25]. However, in the early 2000s, providers adopted a different approach, withholding therapy in patients who were not yet immunosuppressed. This was due to the toxicity of early regimens and the lack of evidence regarding the benefits of therapy for those with normal CD4 T cell counts. The ensuing decade resulted in substantially advances in the HIV therapy. Today, there are at least 30 HIV medicines currently approved by the U.S. Food and Drug Administration (FDA) to treat HIV, broken up into seven classes, depending on how the drug interferes with the HIV life cycle. According to the European AIDS Clinical Society, people living with HIV's (PLWH) initial antiretroviral therapy (ART) regimen should contain three HIV medicines from at least two different HIV drug classes [26]. The main goal of ART is to suppress HIV RNA to levels undetectable by an HIV Nucleic Acid Amplification Test.

The Strategic Timing of AntiRetroviral Treatment (START) study, a large-scale randomised clinical trial, confirmed the benefits of initiating an ART regimen immediately, irrespective of CD4 T cell count, even when it is greater than 500/mm3 [27]. Early ART conveys a double benefit. It improves the health of individuals (fewer serious AIDS and non-AIDS events) and, by lowering their viral load (HIV RNA), reduces the risk they will transmit the virus to others [1]. These findings prompted changes to national and international guidelines on when to start ART, ushering in the current treatment era [3].

1.2. Cascade of care in Europe, France and Nouvelle Aquitaine

Clinical and public health guidelines now call for all PLWH to be diagnosed early, linked to and engaged in care, and receiving and adherent to ART. France was among the first countries to endorse and enact this policy [7]. This HIV care continuum underpins the UNAIDS' 90-90-90 targets to end HIV as a public health threat by 2030. The UNAIDS' targets call for 90% of people infected with HIV to be diagnosed, 90% of those diagnosed to be on ART and 90% of those receiving ART to achieve viral suppression [28]. These targets have been adopted as a metric of health system performance, showing where improvements are needed and thus where attention and resources should be directed [29].

Western European countries and regions have been among the first to achieve the 90-90-90 targets [30]. In France, the HIV epidemic remains active and heterogeneous, with substantial variation by region and population in HIV incidence, undiagnosed HIV prevalence and time from infection to diagnosis [31]. In 2013, the number of PLWH was estimated at 153,400 (95% CI 150 300 – 156 200), of whom 84% knew their HIV status and were engaged in care; 75% had been on ART for more than six months and 68% had an undetectable viral load (<50 copies/ml) [7]. Providing care early remains a formidable public health challenge since, according to 2010/13 estimates, one in two people had AIDS or CD4 T cell count of <350/mm3 at the time of presentation in care, compromising their long-term prognosis [32, 33].

In our region, the Nouvelle Aquitaine, we estimate that ~92% of those with HIV know their HIV-status and enter care. We also know that 99% of those linked and retained in care are on ART and 92% of them have achieved sustained viral suppression. AIDS-related events are therefore no longer the primary concern of those in care in our region, making HIV a "novel chronic disease" [34].

1.3. Chronic disease management

Sustained viral suppression and improvements in HIV care have normalised PLWH's life expectancies in countries where ART is largely available [22, 35]. They have not, however, enabled their return to a perfect state of health [8]. HIV and associated inflammation, effects of exposure to antiretroviral agents, the high prevalence of modifiable risk factors for age-associated conditions (e.g. smoking) and the effects of other viral co-infections make quality of life (QoL) an ongoing concern [8, 36]. It has been hypothesised that PLWH were at increased risk of age-associated non-communicable comorbidities (AANCC) compared to their HIV-negative counterparts. Recent cross-sectional research on the prevalence of AANCC, conducted within the AGEhIV cohort study, concluded that traditional cardiovascular risk factors (i.e. age, smoking, family history, and waist-

to-hip ratio), but also HIV infection-itself were associated with higher risk of AANCC [37]. PLWH's ongoing care hinges on the prevention, screening and management of multiple age-associated conditions [38]. Multi-morbidity and associated polypharmacy and geriatric syndromes (i.e. falls, urinary incontinence, functional impairment, frailty, sensory impairment, depression and cognitive impairment) threaten to compromise PLWH's health-related quality of life (HRQoL) long before their death [8].

1.4. Beyond chronic disease management

Like others with chronic diseases, PLWH must learn to (re)build their lives [39, 40]. With the availability of effective ART in high-income settings, it became important to consider the physical and psychosocial consequences of HIV on PLWH's daily lives. The question of, what were and would be the effects of the "chronicization" of HIV?, was posed. In France, the ANRS (France Recherche Nord & Sud Sida-hiv Hépatites) commissioned a large national survey of PLWH. This survey, ANRS-VESPA, aimed to describe the living conditions and the social situation of PLWH in the post cART era. The ANRS-VESPA survey was conducted in the early 2000s. It was followed by its sister survey, ANRS-VESPA 2, in the late 2000s. The findings of ANRS-VESPA 2 have provided invaluable guidance for future research on the health status of PLWH in France. One of the notable findings, highlighted by the Professor Yeni, was that "while HIV-related health indicators had improved significantly, their subjective health status had changed only marginally since 2003, partly due to frequent comorbidities" [41]. In both VESPA and VESPA 2, financial difficulties and the patient-provider relationship were independently associated with poorer physical and mental QoL, measured using the SF-36 and SF-12 [41]. A review of the literature published in 2014 by Degroote et al. also provided a good summary of studies on the determinants of QoL among PLWH in northern countries [42]. The authors distinguish four main categories of factors: socio-demographic, clinical, psychological and behavioural. However, some of these studies were conducted in the late 1990s or early 2000s, i.e. at a completely different time in the use of ART and HIV management in general. In more recent studies, non-clinical parameters rather than viral load and CD4 T cell count were associated with poorer QoL in PLWH [43]. In the preface of the French national guidelines on HIV, published in 2013, Professor Philippe Morlat also spoke to this point. Morlat called upon providers to "make the lives of PLWH as harmonious as possible, addressing not only their physical but also their psychological and social well-being, ensuring that those with HIV, including adolescents and children, live in a state of good health as understood by the World Health Organisation (WHO)" [4].

1.5. Quality of life, Health-related quality of life, Patient-reported outcomes

The WHO defined health in 1948 as a “state of complete physical, psychological, and social health and not merely the absence of disease or infirmity”. The notion of QoL emerged from a theoretical framework based on the WHO's holistic definition of health status. In 1994, it was defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [44].

However, many argue that QoL remains ill-defined, taking on different meanings according to the application [45]. In the context of clinical trials, we are concerned with evaluating dimensions of QoL affected by the disease or treatment being studied rather than global QoL. This may sometimes be extended to indirect consequences of disease, such as unemployment or financial difficulties [45]. Facets such as inner peace, hope and optimism, spiritual connection, meaning and purpose, wholeness and integration, awe and inner strength have also been proposed as important in the assessment of QoL [46]. To avoid confusion, the term “health-related” QoL (HRQoL) is often employed, emphasising that we are only interested in health aspects.

QoL and HRQoL are common patient-reported outcomes (PROs). Contrary to QoL, PROs have a clear definition. According to the FDA, they are “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” [47].

1.6. Why measure quality of life and patient-reported outcomes?

Measuring [HR]QoL first became relevant in the context of clinical research. Randomised controlled trials comparing novel therapeutic interventions were interested in understanding their impact not only on survival or other clinically relevant endpoints but also on HRQoL. This is especially true in the case of fatal diseases, where the main goal of a therapeutic intervention is to relieve or prolong the time without symptoms.

HRQoL and PROs assessments more generally have since found other applications. Greenhalgh et al. provides a taxonomy of applications of PROs in clinical practice according to two dimensions: the aggregation of data (either at the level of the individual or group) and the use of PROs data within the clinical consultation or not [48]. At the individual-level, PROs are used to support screening, monitoring, and promoting patient-centred care and, at the group-level, PROs can facilitate clinical decision-making. It has been shown repeatedly in several disease areas that patients’ self-assessment can differ substantially from the judgement of their physicians. PROs have

been shown to enhance patient-provider communication, providing a means for patients to voice their concerns and state their preferences [49].

1.7. How to measure quality of life?

But how does one measure QoL? The short answer is ask the patient. There is a wealth of evidence suggesting that observers, be they providers or carers, are poor judges of patients' opinions and preferences [50]. Providers may base their assessment on more apparent signs of illness (symptoms or toxicity), paying less attention to psychological aspects.

Numerous instruments have been developed to assess QoL in a standardised fashion. These can be broken down into two categories: generic or disease-specific instruments. Generic instruments can be used in multiple conditions/illnesses. Many of the earliest generic instruments prioritise the measurement of people's functional ability, in other words, impairment, disability, or handicap, making the implicit assumption that poorer health means poorer QoL. These generic instruments have the advantage of enabling the comparison of scores between patient populations and the general population. However, they sometimes miss key areas which are of particular concern to a given disease population or lack the sensitivity to detect clinically meaningful differences. This has led to the development of disease-specific instruments.

Be they generic or disease-specific, instruments are comprised of items, used to get at a concept of interest. To capture something that is relatively simple like a well-defined symptom, one item might suffice; whereas, more contentious or less well-defined concepts often require multiple items. Hypothetical constructs that are believed or postulated to exist are represented through models comprising (unobserved) latent variables/traits/factors [45]. We refer to the observed responses to items on a questionnaire as manifest variables. Instruments that measure a single latent trait are referred to as unidimensional. As QoL is a construct that remains somewhat poorly defined, making it a more conceptually complex, many models of QoL are comprised of several latent variables or factors, making them multi-dimensional in nature. It follows that instruments measuring QoL often evaluate several dimensions, each being captured by a single or multi-item scale.

The history of research on QoL in PLWH mirrors that of the epidemic itself. An inventory of HIV-specific PROs, published in 2017, identified 117 publications, covering 72 concepts [51]. Engler et al. distilled these concepts into 12 categories. They note that the category of QoL represented 1/5 of the identified publications or 23 in total, published from 1991 to 2012. Prior to the use of cART, HIV/AIDS was a fatal disease. The first wave of studies on HRQoL were interested in the impact

of HIV/AIDS and its early – largely unsuccessful - treatment on HRQoL. The second wave of studies coincided with the advent of cART. A number of new disease-specific instruments were conceived in response to the rapidly evolving treatment landscape. Many studies from this period focus on the effect of cART on HRQoL. Cooper et al. questioned whether these instruments remain relevant today in a recent systematic review of reviews [52]. They targeted reviews covering the instruments used to measure QoL in adults living with HIV and aimed to identify pragmatic instruments for the assessment of HRQoL in either interventions or clinical care. Like Engler, Cooper identified 23 HIV-specific instruments. They then further selected instruments for review based on their content/comprehensiveness, administration mode/length, and for generic instruments, the availability of normative data.

Cooper et al. deemed the HIV symptom index (SI or SDM) [53], HIV Quality Audit Market (HIV-QAM) [54] and HIV Treatment Satisfaction Questionnaire [55] not comprehensive enough in terms of the breadth of dimensions covered. Nine other instruments took longer than 10 minutes to complete or had more than 40 items.[1] Four scales were excluded due to lack of patient input in their development.[2] The authors ultimately concluded that only seven disease-specific instruments, which were sufficiently comprehensive (covering at least three domains), could be self-administered in 10 minutes or less and had been developed with input from patients. These included: The AIDS Clinical Trials Group (ACTG) SF-21, The HIV-QL31 [56], The Medical Outcomes Study HIV Health Survey (MOS-HIV) [57, 58], The Multidimensional Quality of Life Questionnaire for HIV/AIDS (MQoL-HIV) [59, 60], the PROQOL-HIV [61], The WHOQOL-HIV BREF [13], the HIV-SQUAD [62].

1.8. PROs administration then and now

A plethora of instruments, covering a broad range of health dimensions, were developed between the 1960-90 [63, 64]. Their use, however, was restricted to clinical trials, often as secondary endpoints, and effectiveness research, and, in spite of potential benefits, rarely in routine practice. As early as the mid to late 1990s, Greenhalgh et al. and others hailed the benefits of PRO measures for both clinicians and patients [65], promoting their use as a means of helping physicians detect changes or problems that would have otherwise gone unnoticed. These early proponents of PROs heralded their potentially benefits for shared decision-making and facilitating patient-provider

[1] HIV Overview of Problems Evaluation Scale (HOPES); AIDS Health Assessment Questionnaire (AIDS-HAQ); General Health Assessment Questionnaire (GHSA); HIV-QOL Isituto Superiore di Sanita Quality of Life Survey (ISSQoL); Functional Assessment of HIV Infection (FAHI); Living with HIV scale, WHOQOL-HIV Instrument; HIV/AIDS Targeted quality of life HAT-QOL)
[2] SF-21; HIV Cost and Service Utilisation Study (HCSUS) measures; the Patient Reported Status and Experience (HIV-PARSE); and Supplement to HIV/AIDS surveillance (SHAS QOL module)

communication. A number of practical, methodological and attitudinal barriers nevertheless hampered their use [65].

The practicality of administering (mostly face-to-face or self-administered paper-and-pencil) PROs has been documented as a major barrier to their use. Paper-based approaches require that a physician and/or other staff administer the questionnaire during the consultation and enter and/or analyse data manually, requiring resources to collect, analyse and utilise PROs data. The psychometric properties of instruments were also questioned by providers [66]. They wondered whether instruments measured what they claimed to measure and whether changes in observed scores correspond to changes in objective measures of health status. However, these reservations were more a reflection of their lack of familiarity with PRO measures rather than the instruments themselves. Finally, providers did not see the relevance and the value of psychosocial information generated, considered to be outside the scope of medicine, in their practice. Furthermore, they also questioned whether the formal and notably standardised assessment of QoL was preferable to informal unstandardised assessments. Finally, there was a lack of hard evidence that the use of PROs improved care and outcomes [67].

The intervening years have resolved some but not all of these initial barriers. The practicality of administering PROs has improved with the advent of computer and Internet-based administration as of the early to the mid-2000s. Computerized PRO assessments have become common in settings where PROs have been widely adopted, offering a number of advantages over paper and pencil-and-paper assessments. For example, applying compulsory items and pre-specifying acceptable ranges or values can improve data completeness and quality. Complex skip patterns can be programmed to ease administration. Immediate data capture reduces the burden and/or costs associated with data entry [68]. Furthermore, from a methodological point of view, there is strong evidence to suggest that electronic and paper-and-pencil administration methods of patient-reported outcomes are equivalent [69].

1.9. PROs administration in HIV cohorts and care

To date, to our knowledge, the first examples documenting the collection of PRO measurement into routine HIV care come from the United States. The HIV cohort at the University of Washington was among the first to experiment with systematic computerized collection of patient reported data. Crane et al. described efforts to implement systematic electronic collection of PROs in HIV care, concluding that it was both promising for research and clinical care [9]. The challenges associated

with collecting high quality data in routine care and the limitations of data recorded in patients' medical records or computerized medical records may have been noted by Kozak et al.[10]. The demands of clinical practice and the willingness of patients to disclose sensitive information can compromise the completeness and quality of the data entered in medical records. In their 2012 study, conducted at the University of Alabama HIV/AIDS Clinic in Birmingham, they compared self-reported data with data recorded in the electronic medical record (EMR) and examined the association between substance abuse, depression and poor ART adherence among PLWH. Not only did the authors document significant differences in the prevalence of self-reported substance use and depression compared to those documented in the EMR, but they found that self-reported measures rather than those documented in the EMR were better correlated with poorer ART adherence [10]. This research suggests that collecting PROs is an alternative and potentially more reliable way to capture data in sensitive areas such as alcohol and other drug use. In addition, patient reported data can help clinicians identify problems at the time of care, as demonstrated by Lawrence et al. [70]. As part of the same University of Alabama HIV/AIDS Clinic initiative, patient reported data were used to detect suicidal thoughts and trigger an automated page for predetermined caregivers who performed more detailed psychological assessments [70]. In addition to these examples, there is ongoing experimentation of the use of PROs in care both in Europe, namely the Happi application [https://happiapp.nl/happiapp-en.html], The EmERGE Project [https://www.emergeproject.eu/], the HIVOutcomes initiative [http://hivoutcomes.eu/about-us/], and Canada, speaking to the growing interest in this topic.

2. Objectives and outline of the thesis

This thesis outlines the conception and formative research undertaken to develop a new module for the collection of electronic PROs, including HRQoL within the ANRS Aquitaine Cohort's data capture and information system. I outline the study's conception and protocol, including its larger aims, some of which are beyond the scope of the thesis, in Chapter 1. In Chapter 2, I present the formative research undertaken to ensure that the ePRO module was ready for pilot testing. Chapter 3 outlines the initial pilot phase of the study and presents indictors of acceptability and finally, Chapter 4 presents an analysis of the basic psychometric properties of the WHOQOL-HIV BREF instrument, conducted in preparation for further analysis of the factors associated with HRQoL in the current treatment era.

3. The ANRS CO3 Aquitaine - AQUIVIH Cohort - QuAliV

The ANRS CO3 Aquitaine Cohort was first conceived in 1987 as an epidemiological and clinical surveillance system for HIV in the former Aquitaine region. Clinical, biological, therapeutic and epidemiological data were collected in a standardised fashion from those in care at public hospitals. The ANRS CO3 Aquitaine Cohort initially covered five departments of Bordeaux University Hospital and then extended gradually to other hospitals. The ANRS CO3 Aquitaine cohort sought to understand the HIV's natural history, its management, namely its treatment.

The cohort's scientific agenda has evolved with scientific progress in the field of HIV infection itself and its management. The ANRS Aquitaine Cohort then aimed to study the temporal trends of universal treatment, its determinants and consequences. At the national level, it has contributed the evidence base, hence its certification by the ANRS over the past 30 years. In Europe and beyond, it participated historically in all major international cohort collaborations (CASCADE, COHERE, D:A:D:, EuroSida, EuroCoord, HIV-Causal).

Bordeaux's University Hospital sponsors the cohort in its current iteration, AQUIVIH (Risk of morbidity and evaluation of long-term antiretroviral treatment in people living with HIV in Aquitaine). Its inclusion period spans 2016-2020 and addresses a number of research areas, considered relevant in the current treatment era, one in which it is increasingly important to generate more detailed data on co-morbidities associated with ageing in PLWH. Specifically, the AQUIVIH cohort aims:

- to identify risk factors for infection progression (Deaths, AIDS and non-AIDS events);
- to identify the effectiveness and tolerance of antiretroviral treatments and different prescribed combinations;
- to assess the modalities of care for PLWH and study their impact on the progression of the disease;
- to contribute to hospital epidemiological surveillance of HIV infection management in the region and finally;
- to identify emerging psycho-social issues among PLWH.

As of 2018, the cohort has included more than 10,050 PLWH. The cohort's active follow-up is defined as the number of patients who have had at least one consultation, a traditional hospitalisation or outpatient hospital consultation in one of the participating centres. In 2018, 4,926 patients were being actively followed-up. The mean follow-up time of those in active follow-up was 18±9 years since HIV diagnosis. Twenty-eight percent are women and their average age at the most recent

consultation is 53 years old. Nearly a quarter (24.3%) are over 60 years old. The majority were infected through sexual contact (42.5% are men who have sex with men [MSM] and 38.1% are heterosexuals) and 10.6% through intravenous drug use. 19.9% have been diagnosed with AIDS. 98.4% of PLWH in active follow-up are on ART and, of these, 92% have a viral load <50 copies/mL.

3.1. QuAliV Ancillary Study

The “QuAliV” study was designed as an ancillary study of the current iteration of the ANRS Aquitaine cohort, sponsored by the University Hospital of Bordeaux, is, in its first iteration, a cross-sectional study within the “AQUIVIH” cohort.

Chapter 1: Conception

Article 1: Integrating Electronic Patient-Reported Outcome Measures Into Routine HIV Care and the ANRS CO3 Aquitaine Cohort's Data Capture and Visualization System (QuAliV): Formative Research Study Protocol

Abstract

Background: Effective antiretroviral therapy has greatly reduced HIV-related morbidity and mortality, dramatically changing the demographics of the population of people living with HIV (PLWH). The majority of PLWH in France are well cared for insofar as their HIV infection is concerned but remain at risk for age-associated comorbidities. Their long-term, potentially complex, and growing care needs make the routine, longitudinal assessment of health-related quality of life (HRQoL) and other patient-reported outcomes of relevance in the current treatment era.

Objective: This study aims to describe the development of a Web-based electronic patient-reported outcome (ePRO) system for PLWH linked to patients' ANRS CO3 Aquitaine cohort's data capture and visualization system (ARPEGE) and designed to facilitate the electronic collection of patient-reported data and ultimately promote better patient-physician communication and quality of care (both patient satisfaction and health outcomes).

Methods: Participants who meet the eligibility criteria will be invited to engage with the Web-based patient portal and provided with the information necessary to create a personal patient account. They will then be able to access the patient interface and complete a set of standardized validated questionnaires covering HRQoL (WHOQOL-HIV BREF) and other patient-reported outcomes. The information provided via questionnaires will ultimately be presented in a summary format for clinicians together with the patient's HIV care history.

Results: The prototype of the Web-based ePRO system will be finalized, and the first 2 formative research phases of the study (prototyping, usability testing, and pilot testing) will be conducted from December 2017 to May 2018. We describe the sequential processes planned to ensure that the proposed ePRO system is ready for formal pilot testing, referred to herein as Phases 1a and 1b. We also describe the planned pilot testing designed to evaluate the use and acceptability of the portal from the patient's perspective (Phase 2).

Conclusions: As the underlying information technology solution, ARPEGE, has being developed in-house, should the feasibility study presented here yield promising results, the panel of services provided via the proposed portal could ultimately be expanded and used to experiment with health-promoting interventions in aging PLWH in hospital-based care or adapted for use in other patient populations.

Keywords : patient-reported outcomes; HIV; patient-centered care; health-related quality of life; Patient Generated Health Data

Introduction

The advent of effective antiretroviral therapy (ART) in 1996 in resource-rich settings led to a sharp and rapid decline in AIDS-related deaths [22]. In the following years and now decades, improved treatment options have normalized the survival of people living with HIV (PLWH) [6]. For PLWH to benefit fully from ART, they must be engaged in the continuum or cascade of HIV care. In other words, they must be diagnosed early, linked and retained in care, and receive and adhere to effective therapy [29]. The Joint United Nations Programme on HIV and AIDS' 90-90-90 targets aimed at ending HIV as a public health threat by 2030 are premised on this continuum of care [28]. They call for diagnosing at least 90% of people living with HIV, getting at least 90% of those who are diagnosed on ART, and achieving viral suppression in at least 90% of those who are treated. In settings where the 90-90-90 targets have already been achieved, Lazarus and colleagues have argued that the ultimate goal of HIV care should be to improve health-related quality of life (HRQoL) and have thus proposed a fourth 90%: "achieving good health-related quality of life among 90% of those who are successfully treated for HIV" [71].

This fourth 90% reflects the current needs of the population of PLWH in much of Western Europe, including France, where HIV has become a chronic condition over the most recent decade. The 2013 French HIV Treatment Guidelines first called for addressing the health of PLWH as understood by the World Health Organization's, meaning as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [4]. The concept of HRQoL comes from this definition of health and has become especially relevant to those living with a chronic or recurrent illness.

HRQoL is a common patient-reported outcome (PRO). PRO may be used at the population level for research and improve health care quality and at the individual patient level to support clinical decision-making and ensure the efficient use of resources. However, despite these potential benefits to both clinicians and patients, PROs have yet to be routinely collected or systematically used in routine care by clinicians [72]. This is due to logistical, methodological, and attitudinal barriers [72]. Some of the first studies on the use of PROs in clinical practice have yielded mixed results. There is strong evidence that having patients complete a self-assessment before a medical visit can facilitate communication about HRQoL [48, 73-77]. Yet, the body of evidence on whether this type of exercise alters patient management, affects outcomes, or improves HRQoL or satisfaction is less well understood [78]. Greenhalgh et al have pointed to the lack of theory-driven approaches used to evaluate the use of PRO measures in routine clinical practice and propose that the mechanisms by which the proposed intervention is hypothesized to affect patient outcomes be clearly delineated [79]. Others like Basch et al have argued that the proliferation of robust survey methods coupled with computerized technologies has provided a potentially viable means of collecting this information and ideally integrating it into electronic medical records (EMR) [80]. Computerized and touch-screen technology can substantially

facilitate data collection compared with paper forms, eliminating data-entry and scoring time, and therefore decrease staff burden. Yet, often EMRs and clinical research database systems have been designed to allow for data entry from study staff, making the collection of PROs challenging in some care or research settings [81].

In the context of HIV cohort research, The University of Washington HIV Cohort was among the first to experiment with the routine computerized collection of patient-based measures. Crane et al described efforts to institute the routine collection of electronic PROs (ePROs) in HIV care [9] and Kozak et al highlighted some of the challenges of capturing the high-quality data in routine care and the limitations of data recorded in patients' paper medical or EMR [10]. They note that the demands of clinical care and patients' willingness to disclose sensitive information may compromise the comprehensiveness and the quality of data captured via EMRs. In their 2012 study, conducted at the University of Alabama at Birmingham 1917 HIV/AIDS clinic, they compared self-reported and EMR data and looked at the association between substance abuse, depression, and poor ART adherence in PLWH. Not only did authors document significant differences in the prevalence of self-reported vs EMR-documented substance use and depression, but they found that the self-reported rather than EMR-documented measures were better correlated with poorer ART adherence [10]. This research suggests that ePRO are an alternative and potentially more reliable means of data capture for sensitive domains such as substance use. Furthermore, PROs may help clinicians identify problems at the time of care, as demonstrated by Lawrence et al. [70]. As part of the same initiative at the 1917 HIV/AIDS Clinic, ePROs were used to detect suicidal ideation and trigger an automated page to predetermined clinic personnel who completed more detailed self-harm assessments [70].

Objectives

This paper outlines the formative research protocol being undertaken to develop a Web-based system to collect ePROs linked to the existing data capture infrastructure for those in HIV care in southwestern France. The first aim of the ePRO system is to expand and improve the data collection for the ANRS CO3 Aquitaine Cohort of PLWH being followed up in the 13 public hospitals in the region. The second aim is to make this information available to clinicians in a convenient format together with patients' locally developed, HIV-specific EMR. We describe the sequential process planned to ensure that the proposed ePRO system is ready for formal pilot testing, referred to herein as Phases 1a and 1b. We also describe the planned pilot testing designed to evaluate the use, usefulness, and acceptability of the ePRO system from the perspective of patients (Phase 2). We have outlined the hypothesized changes induced by the inclusion of these data in a locally developed HIV-specific EMR, which is currently being developed.

Methods

Study Design(s)

The ANRS CO3 Aquitaine cohort is an open, prospective hospital-based cohort. The proposed research was conceived as an ancillary study to the cohort. This protocol reports on the sequential study design from the prototyping (Phase 1a) and usability testing (Phase 1b) to piloting (Phase 2). Phases 1a and b rely on mostly qualitative methods. Perspectives of the patient will be assessed and barriers to and facilitators of implementation identified through usability testing. The second phase of the research will initially be based on a cross-sectional study design with the ultimate aim of collecting these data longitudinally (at least once a year) and systematically via the revised ePRO system.

Platform Design

Clinical and laboratory data from medical records have been collected systematically as part of routine care by a team of clinical research associates/technicians from 13 clinics/hospitals throughout the Aquitaine region since the 1980s and via a locally developed information technology (IT) solution, ARPEGE, since 2013. ARPEGE is a secure Web-based data capture and visualization system developed with Microsoft ASP.NET (WebForm). Data are stored within a Microsoft SQL Server 2014-based data management system. A responsive Web-based platform has been designed for patient follow-up within the existing infrastructure of the ANRS CO3 Aquitaine Cohort. This IT solution was originally developed to meet the data collection requirements of the ANRS CO3 Aquitaine Cohort. Unlike the hospital's EMR, which did not allow for data to be visualized nor used for research, ARPEGE provides

HIV physicians with patients' medical histories. Its interoperability with the surrounding health information system infrastructure evolved to allow laboratory data to be downloaded from the Bordeaux University Hospital's laboratory medicine information system, which includes results of all tests performed as part of hospital-based care. The proposed QuAliV ePRO system expands upon this IT solution by developing a flexible interface for the Web-based collection of ePROs both in a hospital setting and beyond (in the patient's home) with a special focus on the presentation of individual patient's results. The inclusion of administrative data from the Program for Medicalizing Information Systems and clinical data from the hospital's EMR is planned but has not yet been completed.

Initial Website Specifications

The primary feature of the ePRO system is the survey feature due to the platform being nested within a longstanding hospital-based cohort study. The first feature is to facilitate data collection on HRQoL and its main determinants via validated electronic questionnaires. The content of the patient interface is based on current treatment guidelines for people being treated for HIV and associated comorbidities [4]. French guidelines recommend an annual checkup, during which a number of issues should be addressed by the HIV physician according to the patients' age and sex. According to the taxonomy of applications of PROs in clinical practice laid out by Greenhalgh, the proposed system aims to optimize this check-up by having the patient complete a standardized self-reported questionnaire before the visit [48]. The proposed ePRO system relies on a selection of validated questionnaires that were mostly already available in French. The questionnaires have already been evaluated individually according to their psychometric properties [82], administration method, and length. The following areas are covered by the ePRO system, broken up into thematic modules covering: socioeconomic status and an individual social and material deprivation (Evaluation de la Précarité et des Inégalités de santé dans les Centres d'Examens de Santé [EPICES]) [12], multidimensional quality of life (WHOQOL-HIV BREF) [13], treatment burden (Treatment Burden Questionnaire) [14], physical activity (The Short Version of the International Physical Activity Questionnaire [IPAQ]), alcohol use and screening for at-risk drinking behaviour (Alcohol Use Disorders Identification Test Consumption [AUDIT-C], Fast Alcohol Consumption Evaluation [FACE]) [15], tobacco and nicotine use and screening for tobacco dependency (Fagerström), cannabis (Cannabis Abuse Screening Test [CAST]) and drug use, and finally, depression (Patient Health Questionniare [PHQ-9]) [16]. The system also allows patients to report any other treatment-related issues in a free-text field. Where applicable, we have followed the recommendations put forth by the International Society for Pharmacoeconomics and Outcomes Research ePRO Task Force on adapting paper-based instruments to ensure that data produced are equivalent or superior to those generated from paper-based administration methods [17]. It should be noted that the choice of questionnaires for the initial prototype is intentionally more exhaustive than the anticipated final version,

as we do not know whether the questionnaires selected will be adequate in terms of their psychometric properties. This will be verified during the pilot phase.

We have planned additional IT security measures including the encryption of email addresses using the Advanced Encryption Standard (AES) encryption algorithm with a key length of 256 bits. AES encryption technology is currently one of the most secure. Passwords will be encrypted by the BCrypt algorithm, which is recognized as being at the cutting edge of hash chain technology. Furthermore, passwords created by the user must contain at least 8 alphanumeric characters including at least 2 special characters, a capital letter, and a number that must be changed every year. The unique study-specific identification number will contain 8 randomly defined alphanumeric characters.

Pre-implementation (Phases 1a and b)

The IT solution, ARPEGE, has been made available in hospital-based HIV care centers since 2013. Its use is facilitated by research assistant technicians. To inform the implementation strategy, taking into account the facilitators and barriers faced by users, a pre-implementation assessment identifying those factors crucial to implementation success or failure will be conducted before determining the final implementation procedure.

Phase 1a: Prototyping (Eliciting Feedback on Initial Specifications)

Based on the above specifications, a preliminary version of the interface will be constructed and presented to patients and clinicians to elicit their feedback. The aim of the preliminary qualitative interviews is not to rigorously evaluate the website's performance but to obtain information that could be used to develop the interface and prepare it for formal pilot testing. The interviewer will present a mock-up of the Web-based patient interface and describe its proposed functions to each participant.

Phase 1b: Usability Testing

Usability measures to what extent a person can use a system for its goal effectively, efficiently, and satisfactorily [83]. Usability testing will be conducted on the prototype of the ePRO system according to guidelines from the website Usability.gov [84]. A convenience sample of 10 patients will be recruited and interviewed in an outpatient hospital setting. This sample is considered adequate to evaluate whether the website is ready for planned, more rigorous, pilot testing [85]. Eligible patients, identified by clinical staff, will be approached for the study before their scheduled visit. During usability testing, patients will access the website and test its features, including the site login, survey completion, and review of results. Patients will "think aloud" as they complete the login process and survey and complete a semistructured

interview about the ease of use and completion, presence of mistakes or problems, user satisfaction, likes/dislikes, and their willingness to use it regularly before visits. Efficiency (eg, time it takes to complete tasks) will also be monitored. Finally, participants will also be asked to complete the System Usability Scale (SUS), a validated 10-item scale with Likert-scaled responses ranging from "strongly agree" to "strongly disagree" and a summary score [84] .

The findings from this first phase (1a and b) will inform the second phase of the study, which will extend the implementation of the proposed patient interface in a limited number of hospitals and aim to evaluate its use and acceptability.

Phase 2: Pilot Testing

Proposed Setting

The study will be carried out in the ANRS CO3 Aquitaine Cohort, an open, prospective, hospital-based cohort of PLWH followed-up in 13 clinics in southwestern France. The pilot testing will take place in 3 of them, selected to reflect variations in resources (human and material) or geographic setting (rural vs urban clinics). We aim to assess the acceptability of the proposed system in different clinical contexts to eventually offer center-specific adjustments to the proposed implementation procedures.

Inclusion and Exclusion Criteria (Phase 2)

As this study will be nested within a longstanding existing hospital-based cohort of PLWH, those invited to participate in this study must meet the cohort's eligibility criteria: aged 18 years or older, confirmed HIV-1 diagnosis, and having signed a consent form. Access to a personal email account and the Internet via either a computer or smartphone in a private setting will be verified by the clinician before the participant is invited to engage with ePRO system. Patients who express an interest in completing a self-reported questionnaire but lack either a personal computer or smartphone and/or reliable Internet access will be provided with a paper version questionnaire or, depending on the study center, invited to use a study-specific electronic tablet (Samsung Galaxy Tab S2).

Patient Selection and Recruitment

Patient selection and recruitment will be done in tandem with planned administrative changes to the cohort and will take place during routine care. The standard operating procedures detailing the new procedures for including participants in this component of the cohort have been developed during

successive team meetings. Before each visit, on-site research assistants will provide clinicians with a study-specific randomly generated patient identifier (Figure 1).

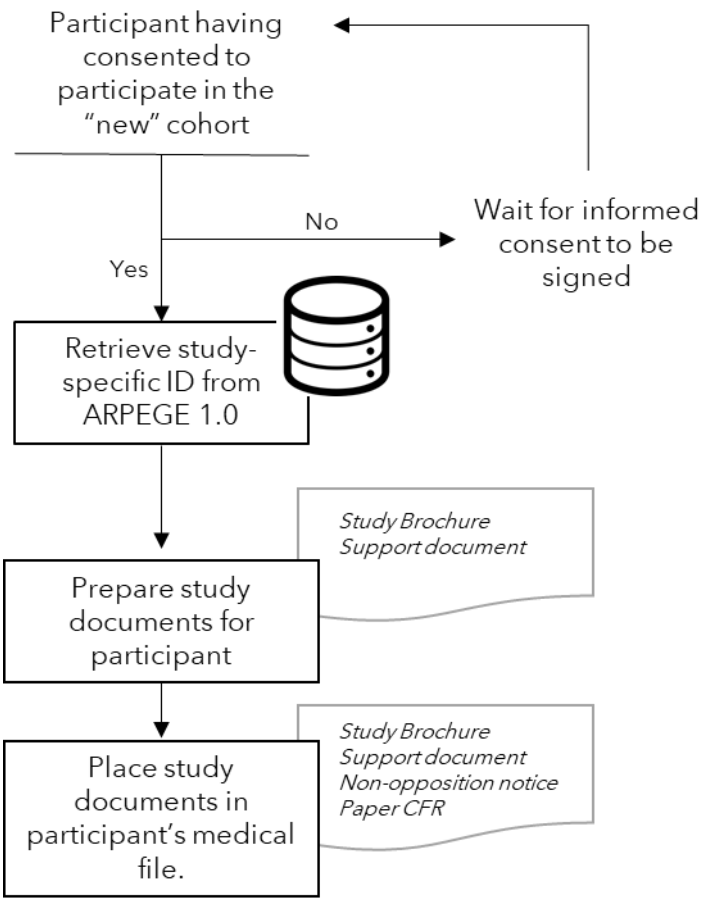

FIGURE 1: PRE-VISIT PREPARATION OF FILES FOR THEORETICALLY ELIGIBLE PARTICIPANTS.

Clinicians will invite patients to participate in the ANRS CO3 Aquitaine cohort's new research initiative at the time of the consultation (Annex VIII for details). Figure 2: Integration of the QuAliV ePROs module outlines the integration of the QuAliV patient portal in the ANRS CO3 Aquitaine Cohort.

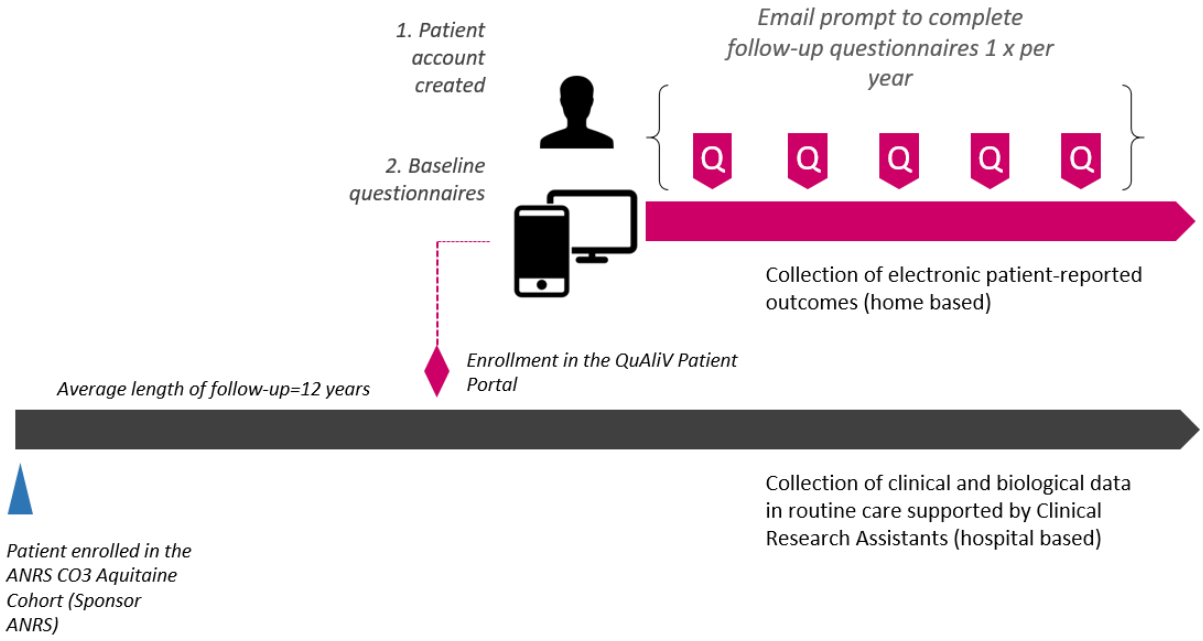

FIGURE 2: INTEGRATION OF THE QUALIV EPROS MODULE

Once the eligibility criteria have been verified, if the patient wishes to participate in the study, he/she will be provided with a patient-oriented brochure developed specifically for those interested in engaging with the system. The study-specific identifier required for participants to create their accounts will then be noted on a detachable part of the patient-oriented brochure for easy reference. This study-specific identifier is required to create an account via ARPEGE. It allows for the patient account and the self-reported data to be linked to the existing clinical data capture and visualization system (ARPEGE). As the patients could be accessing the website from their phones or from their home computers, the section of the brochure for noting the study-specific identifier will be detachable, allowing the study participant to leave the brochure at the hospital for the sake of confidentiality (Annex III). To monitor study enrolment and ascertain whether the proposed system is acceptable to users, enrolment will be tracked by the centers.

Eligible participants will be directed to the study website (Annex VI) where they will be provided with additional details about the research initiative and its aims. The website will provide additional information to “recruited” patients, encouraging them to take a more active role in his or her HIV care and well-being. The patient will be redirected to the account creation page, powered by ARPEGE. To ensure that the participant created his/her account successfully, he/she will be asked to enter his/her email twice together with the unique patient identifier. The patient will then be asked to confirm his/her email address before he/she can access the patient portal. Metadata will be monitored to identify any bottlenecks during the pilot phase.

Study Population

The cohort's "active follow-up" is defined as patients who have been seen over the course of the previous year either at a hospital-based consultation or been hospitalized. In 2016, approximately 4480 patients were actively being followed-up in the cohort. The average length of follow up is 12 years post HIV diagnosis. In total, 27.95% (1252/4480) of the cohort is female and mean age is 51 years (SD=11 years). The majority of the cohort contracted HIV through sex (41.93% (1881/4486) are men who have sex with men and 37.09% (1664/4486) are heterosexuals) and 12.75% (572/4486) through injection drug use. Moreover, 20.60% (923/4480) of those in active follow-up have been diagnosed with AIDS, 26.70% (1010/3745) are overweight, and 8.62% (323/3745) are obese. In addition, 43.71% (1831/4189) report being current smokers.

Statistical Analysis

Feedback on initial specification from patients will be evaluated qualitatively during Phase 1a. During Phase 1b, in addition to qualitative feedback provided using the "think aloud" approach and semi-structured interview, we will define success in usability a priori as SUS score reaching a ceiling effect: with a minimum score of 70 - as the generally accepted cut-off usability rating for "good" [83]. For each measure, we will also calculate the percentage of completed items by the total number of items for each PROs module.

To evaluate the use of the ePRO interface, we will monitor eligibility, QuAliV numbers issued, accounts created, and initial questionnaires completed within 1 month of the visit. The following process indicators will be used to assess acceptability:

1. the proportion of people who refused to participate in the study
2. the proportion of those who received information but failed to create an account
3. the proportion of those who created an account but failed to complete the questionnaires.

To assess acceptability, the main outcomes of interest of the Phase 2 study are the overall participation rate (proportion of those who created and account and completed the assessment) implemented as a pilot and the participation rates based on readily available personal, demographic, and treatment-related factors. Differences based on age, sociodemographic characteristics, and clinic and transmission groups will be evaluated using the chi-square test. Determinants of use will be evaluated using logistic regression methods.

As all the questionnaires will be used in an electronic form, the psychometric properties of the instruments included in the patient portal will also be verified. We will be especially attentive to the presence of floor and ceiling effects. We will also monitor the time it takes to complete the questionnaire as a further indicator of feasibility. The dimension of HRQoL measured by the instruments will be assessed using confirmatory factor analysis.

Finally, we will use the pilot phase to verify the distribution of the main outcome of interest (HRQoL) of our epidemiological study, seeking to measure both the prevalence and the determinants of poorer HRQoL in PLWH in the current HIV treatment era. We will use this initial sample to calculate the required sample size and plan for the scale up of the platform in all of the participating hospitals/clinics in the region.

Ethical and Legal Aspects

The implementation of this study called for an amended version of the cohort protocol to be submitted to an ethics committee. This amendment entailed a detailed description of the content of the questionnaires included in the ePRO system, the content of patient-oriented brochure and the external patient-oriented website. Approval was granted in August 2017.

As the implementation of this system requires patients to use their email addresses to create their personal accounts, an amendment to the regulatory authorizations previously granted to the cohort by The French National Commission on Informatics and Liberty, an independent administrative regulatory body charged with ensuring that data privacy laws are applied to the collection, storage, and use of personal data, was requested in late 2017 and approval was granted on March 12, 2018.

Results

Proposed Timelines and Future Research

Seed funding was granted by France REcherche Nord&Sud Sida-hiv Hépatites (ANRS) in 2017 via the CSS-5 call in January, 2017 and additional staff recruited in June 2017 to develop the ePRO system's infrastructure. DB was awarded a 36-month "young researcher" grant from Sidaction to design and conduct this study within the ANRS CO3 Aquitaine cohort as part of her doctoral research.

The development of the prototype of QuAliV ePRO system and the first 2 phases of the study will be conducted between December 2017 and May 2018. The results from Phase 1 will ultimately inform the

implementation of the pilot project. Efforts to integrate data generated from the ePROs system into a HIV-specific EMR will begin in April 2018 as part of the next phase of APREGE's development. Enrolment of participants is planned in June 2018.

Discussion

Although France boasts a robust public health and epidemiological surveillance system, its cohorts relied, until recently, on paper-based data collection methods. The Aquitaine cohort, launched in 1987, transitioned to an electronic Case Report Form supported by center-based clinical research technicians in 2013. The relatively recent transition to an electronic data capture and visualization system has made the collection of ePROs in hospital-based cohort studies of PLWH conceivable and timely in light of the current HIV care paradigm in France. The introduction of the proposed ePRO system and updated physician HIV-specific EMR, presenting a summary of patients' clinical, laboratory, and self-reported records, will imply changing both patient behavior and daily clinical practice.

In line with recommendations put forth by Greenhalgh and colleagues, we have diagrammed the hypothesized mechanisms by which this patient ePRO system is designed to promote improved patient-physician communication (Figure 2, adapted from Greenhalgh et al) [79]. The results of the self-reported questionnaires will be summarized for clinicians in a convenient format developed in collaboration with end users. We hypothesize that providing this information can improve communication and, thus, lead to better quality of care (both patient satisfaction and health outcomes). Presenting this information will also allow HIV physicians to monitor the patient's response to treatment over time (ART and treatment for associated comorbidities) and/or detect issues that may have previously gone unnoticed (eg, a change in employment status, living conditions, addictions, a lack of social support, depression, and/or a decline in HRQoL). We hypothesize that physicians will also be better equipped to discuss health-promoting behaviors such as exercise or smoking cessation, adjust treatment regimens, or refer patients to a specialist or allied health professionals (eg, therapist, dietician, social worker).

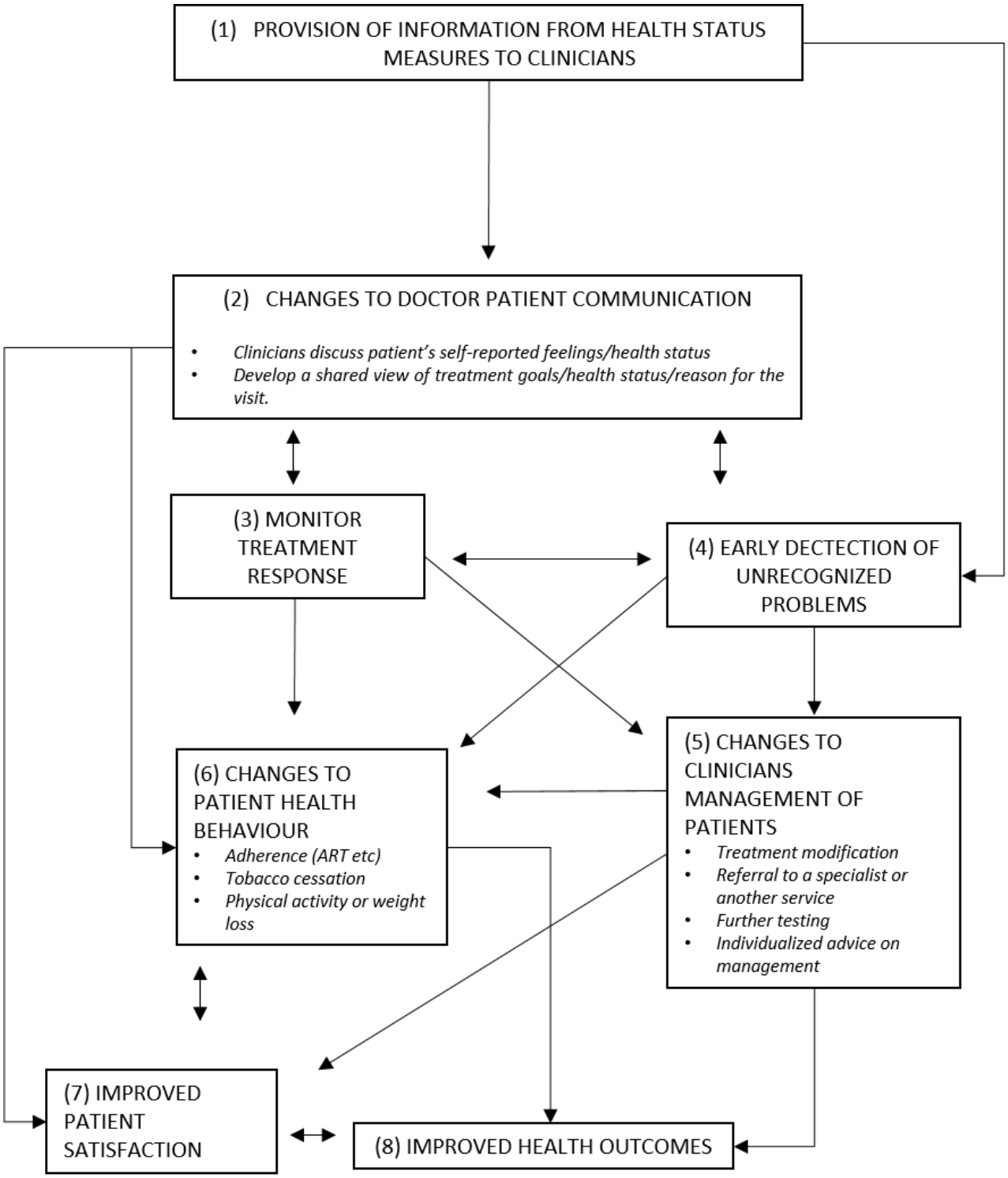

FIGURE 3: HYPOTHESIZED CHANGES TO CLINICAL DECISION-MAKING AS A RESULT OF EPRO

As the underlying IT solution, ARPEGE, was developed in house, should the Phases 1a and b and Phase 2 studies, presented here, yield promising results, the panel of services provided via the proposed ePRO system could ultimately be expanded. For example, continuous patient education/coaching for better self-management, similar to interventions that have been implemented for other chronic conditions (diabetes, heart disease, etc), could be offered, as could decentralized models of care and/or facilitated communication with one's general practitioner. The adoption of these different services could ultimately be the aim of future experimental research in this patient population aging with HIV. Alternatively, the proposed system, designed for outpatient hospital-based HIV care, could be adapted for use in other chronic diseases and/or other care settings.

Protocol

Integrating Electronic Patient-Reported Outcome Measures into Routine HIV Care and the ANRS CO3 Aquitaine Cohort's Data Capture and Visualization System (QuAliV): Protocol for a Formative Research Study

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Abstract

Background: Effective antiretroviral therapy has greatly reduced HIV-related morbidity and mortality, dramatically changing the demographics of the population of people living with HIV. The majority of people living with HIV in France are well cared for insofar as their HIV infection is concerned but remain at risk for age-associated comorbidities. Their long-term, potentially complex, and growing care needs make the routine, longitudinal assessment of health-related quality of life and other patient-reported outcomes of relevance in the current treatment era.

Objective: We aim to describe the development of a Web-based electronic patient-reported outcomes system for people living with HIV linked to the ANRS CO3 Aquitaine cohort's data capture and visualization system (ARPEGE) and designed to facilitate the electronic collection of patient-reported data and ultimately promote better patient-physician communication and quality of care (both patient satisfaction and health outcomes).

Methods: Participants who meet the eligibility criteria will be invited to engage with the Web-based electronic patient-reported outcomes system and provided with the information necessary to create a personal patient account. They will then be able to access the electronic patient-reported outcomes system and complete a set of standardized validated questionnaires covering health-related quality of life (World Health Organization's Quality of Life Instrument in HIV infection, named WHOQOL-HIV BREF) and other patient-reported outcomes. The information provided via questionnaires will ultimately be presented in a summary format for clinicians, together with the patient's HIV care history.

Results: The prototype of the Web-based electronic patient-reported outcome system will be finalized and the first 2 formative research phases of the study (prototyping and usability testing) will be conducted from December 2017 to May 2018. We describe the sequential processes planned to ensure that the proposed electronic patient-reported outcome system is ready for formal pilot testing, referred to herein as phases 1a and 1b. We also describe the planned pilot-testing designed to evaluate the acceptability and use of the system from the patient's perspective (phase 2).

Conclusions: As the underlying information technology solution, ARPEGE, has being developed in-house, should the feasibility study presented here yield promising results, the panel of services provided via the proposed portal could ultimately be expanded and used to experiment with health-promoting interventions in aging people living with HIV in hospital-based care or adapted for use in other patient populations.

Trial Registration: ClinicalTrials.gov NCT03296202; https://clinicaltrials.gov/ct2/show/NCT03296202 (Archived by WebCite at http://www.webcitation.org/6zgOBArps)

Registered Report Identifier: RR1-10.2196/9439

(JMIR Res Protoc 2018;7(6):e147) doi:10.2196/resprot.9439

KEYWORDS

patient-reported outcomes; HIV; patient-centered care; health-related quality of life; patient-generated health data

Introduction

Background

The advent of effective antiretroviral therapy (ART) in 1996 in resource-rich settings led to a sharp and rapid decline in AIDS-related deaths [1]. In the following years and now decades, improved treatment options have normalized the survival of people living with HIV (PLWH) [2]. For PLWH to benefit fully from ART, they must be engaged in the continuum or cascade of HIV care. In other words, they must be diagnosed early, linked and retained in care, and receive and adhere to effective therapy [3]. The Joint United Nations Programme on HIV and AIDS' 90-90-90 targets aimed at ending HIV as a public health threat by 2030 are premised on this continuum of care [4]. They call for diagnosing at least 90% of people living with HIV, getting at least 90% of those who are diagnosed on ART, and achieving viral suppression in at least 90% of those who are treated. In settings where the 90-90-90 targets have already been achieved, Lazarus and colleagues have argued that the ultimate goal of HIV care should be to improve health-related quality of life (HRQoL) and have thus proposed a fourth 90%: "achieving good health-related quality of life among 90% of those who are successfully treated for HIV" [5].

This fourth 90% reflects the current needs of the population of PLWH in much of Western Europe, including France, where HIV has become a chronic condition over the most recent decade. The 2013 French HIV Treatment Guidelines first called for addressing the health of PLWH as understood by the World Health Organization, meaning as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [6]. The concept of HRQoL comes from this definition of health and has become especially relevant to those living with a chronic or recurrent illness.

HRQoL is a common patient-reported outcome (PRO). PROs may be used at the population level for research and to improve health care quality and at the individual patient level to support clinical decision-making and ensure the efficient use of resources. However, despite these potential benefits to both clinicians and patients, PROs have yet to be routinely collected or systematically used in routine care by clinicians [7]. This is due to logistical, methodological, and attitudinal barriers [7]. Some of the first studies on the use of PROs in clinical practice have yielded mixed results. There is strong evidence that having patients complete a self-assessment before a medical visit can facilitate communication about HRQoL [8-13]. Yet, the body of evidence on whether this type of exercise alters patient management, affects outcomes, or improves HRQoL or satisfaction is less well understood [14]. Greenhalgh et al have pointed to the lack of theory-driven approaches used to evaluate the use of PRO measures in routine clinical practice and propose that the mechanisms by which the proposed intervention is hypothesized to affect patient outcomes be clearly delineated [15]. Others like Basch et al have argued that the proliferation of robust survey methods coupled with computerized technologies has provided a potentially viable means of collecting this information and ideally integrating it into electronic medical records (EMR) [16]. Computerized and touch-screen technology can substantially facilitate data collection compared with paper forms, eliminating data-entry and scoring time, and therefore decrease staff burden. Yet, often EMRs and clinical research database systems have been designed to allow for data entry from study staff, making the collection of PROs challenging in some care or research settings [17].

In the context of HIV cohort research, The University of Washington HIV Cohort was among the first to experiment with the routine computerized collection of patient-based measures. Crane et al described efforts to institute the routine collection of electronic PROs (ePROs) in HIV care, concluding that it was both promising for research and clinical care [18]. Whereas Kozak et al highlighted some of the challenges of capturing high-quality data in routine care and the limitations of data recorded in patients' paper medical or EMR [19]. They note that the demands of clinical care and patients' willingness to disclose sensitive information may compromise the comprehensiveness and the quality of data captured via EMRs. In their 2012 study, conducted at the University of Alabama at Birmingham 1917 HIV/AIDS clinic, they compared self-reported and EMR data and looked at the association between substance abuse, depression, and poor ART adherence in PLWH. Not only did authors document significant differences in the prevalence of self-reported vs EMR-documented substance use and depression, but they found that the self-reported rather than EMR-documented measures were better correlated with poorer ART adherence [19]. This research suggests that ePRO are an alternative and potentially more reliable means of data capture for sensitive domains such as substance use. Furthermore, ePROs may help clinicians identify problems at the time of care, as demonstrated by Lawrence et

al [20]. As part of the same initiative at the 1917 HIV/AIDS Clinic, ePROs were used to detect suicidal ideation and trigger an automated page to predetermined clinic personnel who completed more detailed self-harm assessments [20].

Objectives

This paper outlines the formative research protocol being undertaken to develop a Web-based system to collect ePROs linked to the existing data capture infrastructure for those in HIV care in southwestern France. The first aim of the ePRO system is to expand and improve the data collection for the ANRS CO3 Aquitaine Cohort of PLWH being followed up in the 13 public hospitals in the region. The second aim is to make this information available to clinicians in a convenient format together with patients' locally developed, HIV-specific EMR. We describe the sequential process planned to ensure that the proposed ePRO system is ready for formal pilot testing, referred to herein as phases 1a and 1b. We also describe the planned pilot testing designed to evaluate the acceptability and use of the ePRO system from the perspective of patients (phase 2). We have outlined the hypothesized changes induced by the inclusion of these data in a locally developed HIV-specific EMR, which is currently being developed.

Methods

Study Designs

The ANRS CO3 Aquitaine cohort is an open, prospective hospital-based cohort. The proposed research was conceived as an ancillary study to the cohort. This protocol reports on the sequential study design from the prototyping (phase 1a) and usability testing (phase 1b) to piloting (phase 2). Phases 1a and 1b rely on mostly qualitative methods. Perspectives of the patient will be assessed and barriers to and facilitators of implementation identified through usability testing. The second phase of the research will initially be based on a cross-sectional study design with the ultimate aim of collecting these data longitudinally (at least once a year) and systematically via the revised ePRO system.

Platform Design

Clinical and laboratory data from medical records have been collected systematically as part of routine care by a team of clinical research associates/technicians from 13 clinics/hospitals throughout the Aquitaine region since the 1980s and via a locally developed information technology (IT) solution, ARPEGE, since 2013. ARPEGE is a secure Web-based data capture and visualization system developed with Microsoft ASP.NET (WebForm). Data are stored within a Microsoft SQL Server 2014-based data management system. A responsive Web-based platform has been designed for patient follow-up within the existing infrastructure of the ANRS CO3 Aquitaine Cohort. This IT solution was originally developed to meet the data collection requirements of the ANRS CO3 Aquitaine Cohort. Unlike the hospital's EMR, which did not allow for data to be visualized nor used for research, ARPEGE provides HIV physicians with patients' medical histories. Its interoperability with the surrounding health information system infrastructure has evolved to allow laboratory data to be downloaded from the Bordeaux University Hospital's laboratory medicine information system, which includes results of all tests performed as part of hospital-based care. The proposed QuAliV ePRO system expands upon this IT solution by developing a flexible interface for the Web-based collection of ePROs both in a hospital setting and beyond (in the patient's home) with a special focus on the presentation of individual patient's results. The inclusion of administrative data from the Program for Medicalizing Information Systems and clinical data from the hospital's EMR is planned but has not yet been completed.

Initial Website Specifications

The primary feature of the ePRO system is the survey feature due to the platform being nested within a longstanding hospital-based cohort study. The first feature is to facilitate data collection on HRQoL and its main determinants via validated electronic questionnaires. The content of the patient interface is based on current treatment guidelines for people being treated for HIV and associated comorbidities [6]. French guidelines recommend an annual checkup, during which a number of issues should be addressed by the HIV physician according to the patients' age and sex. According to the taxonomy of applications of PROs in clinical practice laid out by Greenhalgh, the proposed system aims to optimize this checkup by having the patient complete a standardized self-reported questionnaire before the visit [10]. The proposed ePRO system relies on a selection of validated questionnaires that were mostly already available in French. The questionnaires have already been evaluated individually according to their psychometric properties, administration method, and length. The following areas are covered by the ePRO system, broken up into thematic modules covering: socioeconomic status and individual social and material deprivation (Evaluation de la Précarité et des Inégalités de santé dans les Centres d'Examens de Santé [EPICES]) [21], multidimensional quality of life (WHOQOL-HIV BREF) [22], treatment burden (Treatment Burden Questionnaire) [23], physical activity (The Short Version of the International Physical Activity Questionnaire [IPAQ]), alcohol use and screening for at-risk drinking behavior (Alcohol Use Disorders Identification Test Consumption [AUDIT-C], Fast Alcohol Consumption Evaluation [FACE]) [24], tobacco and nicotine use and screening for tobacco dependency (Fagerström), cannabis (Cannabis Abuse Screening Test [CAST]) and drug use, and finally, depression (Patient Health Questionniare [PHQ-9]) [25]. The system also allows patients to report any other treatment-related issues in a free-text field. Where applicable, we have followed the recommendations put forth by the International Society for Pharmacoeconomics and Outcomes Research ePRO Task Force on adapting paper-based instruments to ensure that data produced are equivalent or superior to those generated from paper-based administration methods [26]. It should be noted that the choice of questionnaires for the initial prototype is intentionally more exhaustive than the anticipated final version, as we do not know whether the questionnaires selected will be adequate in terms of their psychometric properties. This will be verified during the pilot phase.

We have planned additional IT security measures including the encryption of email addresses using the Advanced Encryption Standard encryption algorithm with a key length of 256 bits.

Advanced Encryption Standard encryption technology is currently one of the most secure. Passwords will be encrypted by the BCrypt algorithm, which is recognized as being at the cutting edge of hash chain technology. Furthermore, passwords created by the user must contain at least 8 alphanumeric characters including at least 2 special characters, a capital letter, and a number that must be changed every year. The unique study-specific identification number will contain 8 randomly defined alphanumeric characters.

Preimplementation (Phases 1A and 1B)

The IT solution, ARPEGE, has been made available in hospital-based HIV care centers since 2013. Its use is facilitated by research assistant technicians. To inform the implementation strategy, taking into account the facilitators and barriers faced by users, a preimplementation assessment identifying those factors crucial to implementation success or failure will be conducted before determining the final implementation procedure.

Phase 1A: Prototyping (Eliciting Feedback on Initial Specifications)

On the basis of the above specifications, a preliminary version of the interface will be constructed and presented to patients to elicit their feedback. The aim of the preliminary qualitative interviews is not to rigorously evaluate the website's performance but to obtain information that could be used to develop the interface and prepare it for formal pilot testing. Using a semistructured interview guide, we will interview a convenience sample of 10 HIV patients of varying ages, transmission groups, and genders. During the interview, the interviewer will present a mock-up of the Web-based patient interface and describe its proposed functions to each participant.

Phase 1B: Usability Testing

Usability measures to what extent a person can use a system for its goal effectively, efficiently, and satisfactorily [27]. Usability testing will be conducted on the prototype of the ePRO system according to guidelines from the website Usability.gov [28]. A convenience sample of 10 patients will be recruited and interviewed in an outpatient hospital setting. This sample is considered adequate to evaluate whether the website is ready for planned, more rigorous, pilot testing [29]. Eligible patients, identified by clinical staff, will be approached for the study before their scheduled visit. During usability testing, patients will access the website and test its features, including the site login, survey completion, and review of results. Patients will "think aloud" as they complete the login process and survey and complete a semistructured interview about the ease of use and completion, presence of mistakes or problems, user satisfaction, likes/dislikes, and their willingness to use it regularly before visits. Efficiency (eg, time it takes to complete tasks) will also be monitored. Finally, participants will also be asked to complete the System Usability Scale (SUS), a validated 10-item scale with Likert-scaled responses ranging from "strongly agree" to "strongly disagree" and a summary score [28].

The findings from this first phase (1a and 1b) will inform the second phase of the study, which will extend the implementation of the proposed patient interface in a limited number of hospitals and aims to evaluate its acceptability and use.

Phase 2: Pilot Testing

Proposed Setting

The study will be carried out in the ANRS CO3 Aquitaine Cohort, an open, prospective, hospital-based cohort of PLWH followed-up in 13 clinics in southwestern France. The pilot testing will take place in 3 of them, selected to reflect variations in resources (human and material) or geographic setting (rural vs urban clinics). We aim to assess the acceptability of the proposed system in different clinical contexts to eventually offer center-specific adjustments to the proposed implementation procedures.

Inclusion and Exclusion Criteria (Phase 2)

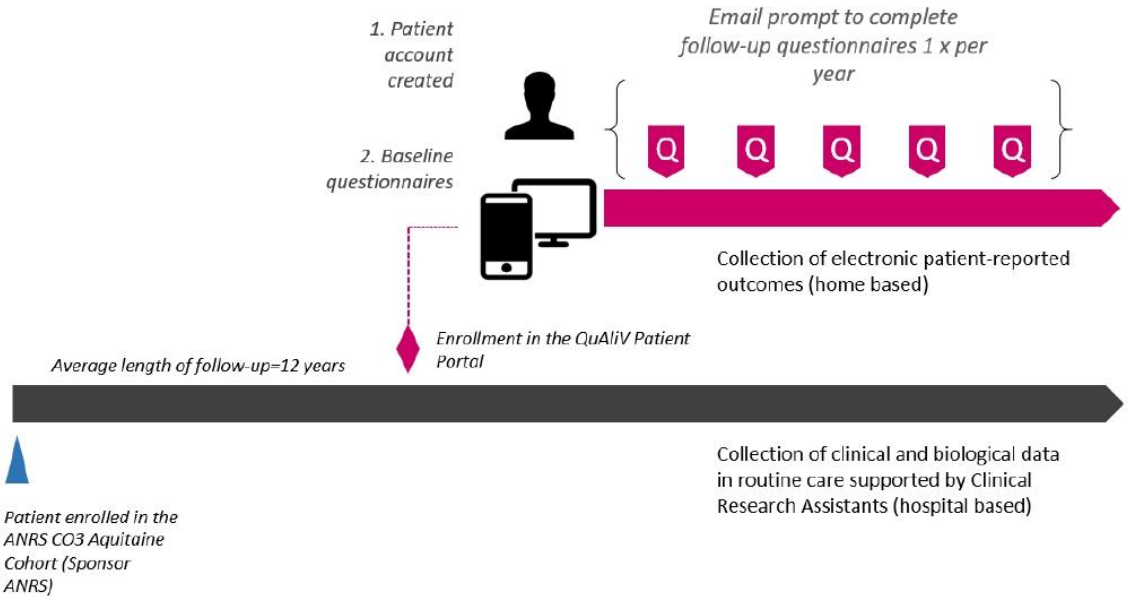
As this study will be nested within a longstanding existing hospital-based cohort of PLWH, those invited to participate in this study must meet the cohort's eligibility criteria: aged 18 years or older, confirmed HIV-1 diagnosis, and having signed a consent form. Access to a personal email account and the internet via either a computer or smartphone in a private setting will be verified by the clinician before the participant is invited to engage with ePRO system. Patients who express an interest in completing a self-reported questionnaire but lack either a personal computer or smartphone and/or reliable internet access will be provided with a paper version questionnaire or, depending on the study center, invited to use a study-specific electronic tablet (Samsung Galaxy Tab S2).

Patient Selection and Recruitment

Patient selection and recruitment will be done in tandem with planned administrative changes to the cohort and will take place during routine care. The standard operating procedures detailing the new procedures for including participants in this component of the cohort have been developed during successive team meetings. Before each visit, on-site research assistants will provide clinicians with a study-specific randomly generated patient identifier. Clinicians will invite patients to participate in the ANRS CO3 Aquitaine cohort's new research initiative at the time of the consultation. Figure 1 outlines the integration of the QuAliV patient portal in the ANRS CO3 Aquitaine Cohort.

Once the eligibility criteria have been verified, if the patient wishes to participate in the study, he/she will be provided with a patient-oriented brochure developed specifically for those interested in engaging with the system. The study-specific identifier required for participants to create their accounts will then be noted on a detachable part of the patient-oriented brochure for easy reference. This study-specific identifier is required to create an account via ARPEGE. It allows for the patient account and the self-reported data to be linked to the existing clinical data capture and visualization system (ARPEGE).

Figure 1. Integration of the QuAliV patient portal in the ANRS CO3 Aquitaine Cohort.



As the patients could be accessing the website from their phones or from their home computers, the section of the brochure for noting the study-specific identifier will be detachable, allowing the study participant to leave the brochure at the hospital for the sake of confidentiality (Multimedia Appendix 1). To monitor study enrollment and ascertain whether the proposed system is acceptable to users, enrollment will be tracked by the centers.

Eligible participants will be directed to the study website where they will be provided with additional details about the research initiative and its aims. The website will provide additional information to "recruited" patients, encouraging them to take a more active role in his or her HIV care and well-being. The patient will be redirected to the account creation page, powered by ARPEGE. To ensure that the participant created his/her account successfully, he/she will be asked to enter his/her email twice together with the unique patient identifier. The patient will then be asked to confirm his/her email address before he/she can access the patient portal. Metadata will be monitored to identify any bottlenecks during the pilot phase.

Study Population

The cohort's "active follow-up" is defined as patients who have been seen over the course of the previous year either at a hospital-based consultation or been hospitalized. In 2016, approximately 4480 patients were actively being followed-up in the cohort. The average length of follow up is 12 years post HIV diagnosis. In total, 27.95% (1252/4480) of the cohort is female and mean age is 51 years (SD 11 years). The majority of the cohort contracted HIV through sex (41.93% (1881/4486) are men who have sex with men and 37.09% (1664/4486) are heterosexuals) and 12.75% (572/4486) through injection drug use. Moreover, 20.60% (923/4480) of those in active follow-up have been diagnosed with AIDS, 26.70% (1010/3745) are overweight, and 8.62% (323/3745) are obese. In addition, 43.71% (1831/4189) report being current smokers.

Statistical Analysis

Feedback on initial specification from patients will be evaluated qualitatively during phase 1a. During phase 1b, in addition to qualitative feedback provided using the "think aloud" approach and semistructured interview, we will define success in usability a priori as SUS score reaching a ceiling effect: with a minimum score of 70 as the generally accepted cutoff usability rating for "good" [27]. For each measure, we will also calculate the percentage of completed items by the total number of items for each PROs module.

We will monitor eligibility, QuAliV numbers issued, accounts created, and initial questionnaires completed within 1 month of the visit. The following process indicators will be used to assess acceptability:

- The proportion of people who refused to participate in the study
- the proportion of those who received information but failed to create an account
- The proportion of those who created an account but failed to complete the questionnaires

To assess use, the main outcomes of interest of the phase 2 study are the overall participation rate (proportion of those who created an account and completed the assessment) implemented as a pilot and the participation rates based on readily available personal, demographic, and treatment-related factors. Differences based on age, sociodemographic characteristics (including rural vs urban), and clinic and transmission groups will be evaluated using the chi-square test. Determinants of use will be evaluated using logistic regression methods.

As all the questionnaires will be used in an electronic form, the psychometric properties of the instruments included in the patient portal will also be verified. We will be especially attentive to the presence of floor and ceiling effects (60% of

responses in extreme categories). We will also monitor the time it takes to complete the questionnaire as a further indicator of feasibility. The dimension of HRQoL measured by the instruments will be assessed using confirmatory factor analysis.

Finally, we will use the pilot phase to verify the distribution of the main outcome of interest (HRQoL) of our epidemiological study, seeking to measure both the prevalence and the determinants of poorer HRQoL in PLWH in the current HIV treatment era. We will use this initial sample to calculate the required sample size and plan for the scale up of the platform in all of the participating hospitals/clinics in the region.

Ethical and Legal Aspects

The implementation of this study called for an amended version of the cohort protocol to be submitted to an ethics committee. This amendment entailed a detailed description of the content of the questionnaires included in the ePRO system, the content of patient-oriented brochure and the external patient-oriented website. Approval was granted in August 2017.

As the implementation of this system requires patients to use their email addresses to create their personal accounts, an amendment to the regulatory authorizations previously granted to the cohort by The French National Commission on Informatics and Liberty, an independent administrative regulatory body charged with ensuring that data privacy laws are applied to the collection, storage, and use of personal data, was requested in late 2017 and approval was granted on March 12, 2018.

Results

Seed funding was granted by France REcherche Nord&Sud Sida-hiv Hépatites (ANRS) in 2017 via the CSS-5 call in January, 2017 and additional staff recruited in June 2017 to develop the ePRO system's infrastructure. DB was awarded a 36-month "young researcher" grant from Sidaction to design and conduct this study within the ANRS CO3 Aquitaine cohort as part of her doctoral research.

The development of the prototype of QuAliV ePRO system and the first 2 phases of the study will be conducted between December 2017 and May 2018. The results from phase 1 will ultimately inform the implementation of the pilot project. Efforts to integrate data generated from the ePROs system into a HIV-specific EMR will begin in April 2018 as part of the next phase of APREGE's development. Enrollment of participants is planned in June 2018.

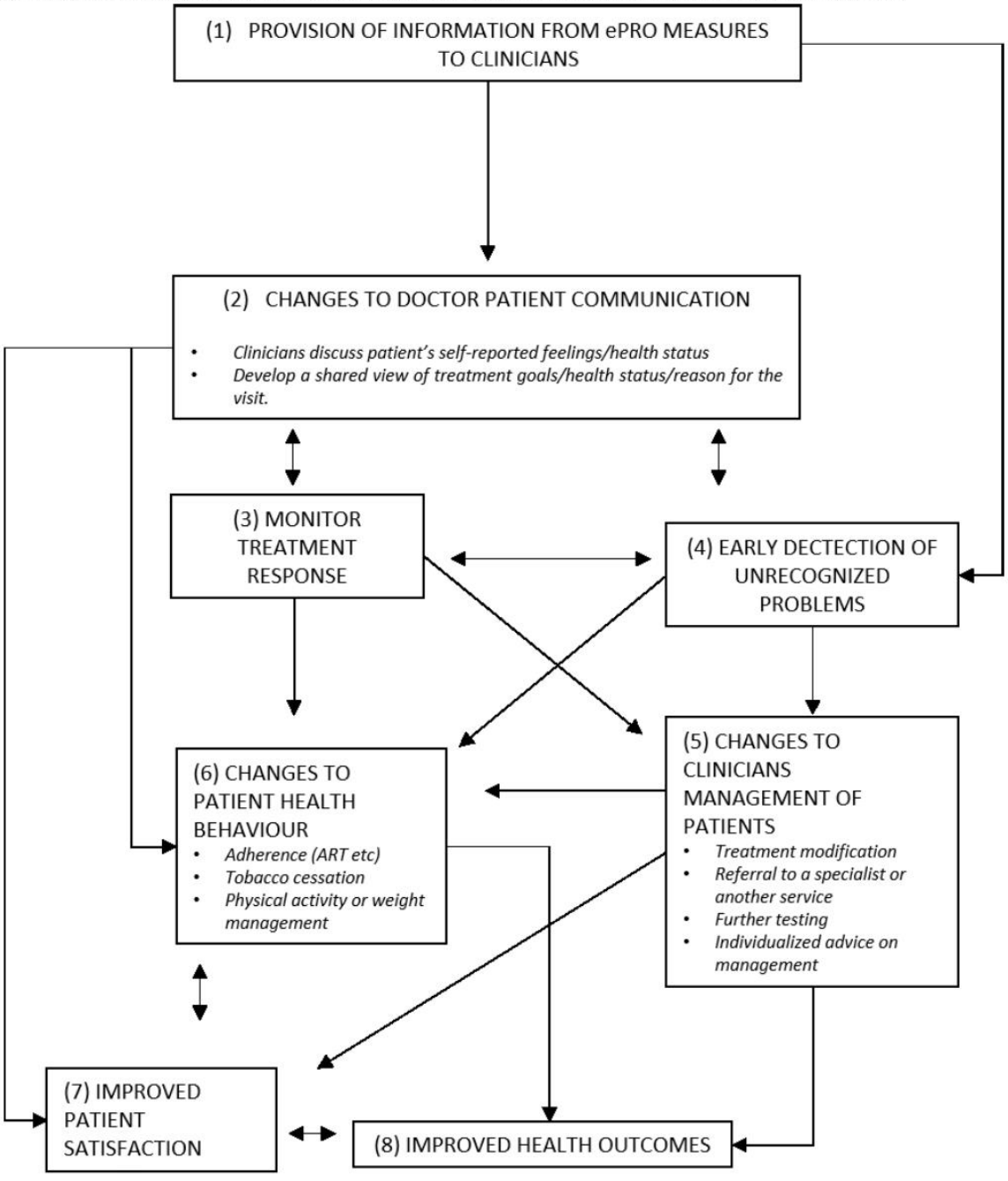
Discussion

Although France boasts a robust public health and epidemiological surveillance system, its cohorts relied, until recently, on paper-based data collection methods. The Aquitaine cohort, launched in 1987, transitioned to an electronic Case Report Form supported by center-based clinical research technicians in 2013. The relatively recent transition to an electronic data capture and visualization system has made the collection of ePROs in hospital-based cohort studies of PLWH conceivable and timely in light of the current HIV care paradigm in France. The introduction of the proposed ePRO system and updated physician HIV-specific EMR, presenting a summary of patients' clinical, laboratory, and self-reported records, will imply changing both patient behavior and daily clinical practice.

In line with recommendations put forth by Greenhalgh and colleagues, we have diagrammed the hypothesized mechanisms by which this patient ePRO system is designed to promote improved patient-physician communication (Figure 2, adapted from Greenhalgh et al) [15]. The results of the self-reported questionnaires will be summarized for clinicians in a convenient format developed in collaboration with end users. We hypothesize that providing this information can improve communication and, thus, lead to better quality of care (both patient satisfaction and health outcomes). Presenting this information will also allow HIV physicians to monitor the patient's response to treatment over time (ART and treatment for associated comorbidities) and/or detect issues that may have previously gone unnoticed (eg, a change in employment status, living conditions, addictions, a lack of social support, depression, and/or a decline in HRQoL). We hypothesize that physicians will also be better equipped to discuss health-promoting behaviors such as exercise or smoking cessation, adjust treatment regimens, or refer patients to a specialist or allied health professionals (eg, therapist, dietician, social worker).

As the underlying IT solution, ARPEGE, was developed in house, should the phases 1a and 1b and phase 2 studies, presented here, yield promising results, the panel of services provided via the proposed ePRO system could ultimately be expanded. For example, continuous patient education/coaching for better self-management, similar to interventions that have been implemented for other chronic conditions (diabetes, heart disease, etc), could be offered, as could decentralized models of care and/or facilitated communication with one's general practitioner. The adoption of these different services could ultimately be the aim of future experimental research in this patient population aging with HIV. Alternatively, the proposed system, designed for outpatient hospital-based HIV care, could be adapted for use in other chronic diseases and/or other care settings.

Figure 2. Hypothesized change to clinical decision making resulting from use of the ePRO system, adapted from Greenhalgh et al.



Acknowledgments

The authors would like to thank the patients, investigators, and clinical research assistants involved in the successful implementation of this study. The authors would also like to thank Alain Volny-Anne and Eugenie Destandau for providing valuable feedback on the design and content and the QuAliV website and ePRO system. The Aquitaine ANRS Cohort is sponsored by the Bordeaux University Hospital and funded by the ANRS (France REcherche Nord&Sud Sida-hiv Hépatites), the Bordeaux University Hospital, and the Inserm U1219 Research Centre.

Conflicts of Interest

DB has received a speaking fee from Gilead. FB declares to have received reimbursement for attending a symposium from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen; speaking fee and consultancy fee from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen; and funds for research from Gilead and ViiV Healthcare. The other authors do not have any conflicts of interest to declare.

Multimedia Appendix 1

Patient-oriented brochure with detachable coupon.

[PNG File, 478KB - resprot_v7i6e147_app1.png]

Multimedia Appendix 2

Conclusions of External Peer-review (English Translation).

[PDF File (Adobe PDF File), 323KB - resprot_v7i6e147_app2.pdf]

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Abbreviations

ART: antiretroviral therapy
EMR: electronic medical records
ePRO: electronic patient reported outcome
HRQoL: health-related quality of life
PLWH: people living with HIV
PRO: patient-reported outcome
WHO: World Health Organization

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Chapter 2: Prototyping & evaluating usability

Article 2: Web-Based Module for the Collection of Electronic Patient-Reported Outcomes in People Living With HIV in Nouvelle Aquitaine, France: Usability Evaluation

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Abstract

Background: Patient-reported outcomes (PROs) can be of great value for both research and chronic disease management. We developed a new module of the ANRS CO3 Aquitaine cohort study's Web-based data capture and visualization solution (APPEGE 2.0) for the collection of electronic PROs among people living with HIV cared for in Nouvelle Aquitaine, France.

Objectives: This study aimed to evaluate the usability of 2 successively developed prototypes of ARPEGE 2.0's electronic PROs module before launching a pilot study, owing to the novelty of the proposed data collection method for our setting and specific characteristics of the target population.

Methods: A total of 2 sequential rounds of empirical, task-based usability evaluations were conducted, involving 8 research staff and then 7 people living with HIV. Evaluators provided written feedback during round 1 and oral feedback during round 2. Evaluators who completed the full set of tasks responded to the System Usability Scale (SUS). We assessed changes in SUS scores between rounds and concluded usability testing when SUS scores reached a ceiling effect, defining good usability a priori as a usability score of 70.

Results: Insights were generated regarding the visibility of system status and the match between the system and the real world that improved the module's usability. Research staff evaluators reported mean SUS scores of 65 (SD 18.87) and patient evaluators reported mean SUS scores of 85 (SD 5.4) P=.032.

Conclusions: Software modifications, informed by successive rounds of usability testing, resulted in sufficient gains in usability to undertake piloting. Insights generated during evaluations prompted us to find the appropriate balance between optimal security and ease of use.

Trial ID number: ClinicalTrials.gov NCT03296202; https://clinicaltrials.gov/ct2/show/NCT03296202 (Archived by WebCite at http://www.webcitation.org/6zgOBArps)

Keywords: PROs, HIV, Usability, health-related quality of life, patient-generated health data

Introduction

HIV, once fatal, is now a manageable chronic illness [34]. In Western Europe, the vast majority of diagnosed HIV-infected individuals are in care and on potent antiretroviral therapy, which prevents serious diseases which are both related and unrelated to AIDS [27]. The improved prognosis and the increased life expectancy of people living with HIV (PLWH) makes preserving health and ensuring good quality of life the cornerstone of their care [6, 71, 86]. One strategy to help providers respond to PLWH's evolving needs and improve the quality and efficiency of their overall care is collecting and using patient-reported outcomes (PROs) [51].

PROs or "any report of the status of the patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [87] have been used extensively in clinical research [51]. PROs can be used at the population level for research and to improve the quality of care or at the individual level to support clinical decision-making [72]. Their use may allow for more accurate symptom detection, better patient-provider communication and improved outcomes [79]. Logistical, technical and ideological barriers have nevertheless limited their use in routine care [68]. The adoption of electronic medical records coupled with the adaptation of paper questionnaires to computerized and Internet-based formats may help overcome these barriers [68, 88].

With evidence from the United States suggesting that the collection of PROs using touchscreen-based information technology was both feasible and of value for both research and clinical HIV care [9, 10, 89], a prototype of an electronic PROs module linked to the ANRS CO3 Aquitaine cohort's data capture and visualization system (ARPEGE® 2.0) was developed in 2017 [11]. As the overall usefulness of interactive health care applications or their usability is likely to affect their acceptability and adoption, usability evaluations of two, successively developed, prototypes of the ARPEGE® 2.0 solution were conducted in preparation for a pilot study [11].

Methods

This formative research study took place in Bordeaux, France at the Inserm UMR 1219- Bordeaux Population Health Research Centre and the St-André Bordeaux University Hospital. It was designed as part of the ANRS CO3 Aquitaine study, an open, prospective hospital-based cohort of PLWH in care in 13 clinics in southwestern France. A local Institutional Review Board approved the study's protocol (Comité de Protection de Personnes Sud-Ouest et Outre-Mer III) on September 18th 2017.

Description of the electronic PROs module powered by ARPEGE® 2.0

ARPEGE® 1.0 is a proprietary, secure, electronic Case Report Form developed in Microsoft ASP.NET (WebForm). Data are stored within a Microsoft SQL Server 2014-based data management system. The ANRS CO3 Aquitaine cohort relies on ARPEGE® 1.0 for data capture. Clinical data, extracted from both medical records, and laboratory data, derived from the hospital's laboratory information management systems, have been collected systematically since 1987 and electronically via ARPEGE® 1.0 since 2013 with the support of Clinical Research Associates. ARPEGE® 2.0 is a generic web-based data capture and visualization system also developed in Microsoft ASP.NET (WebForm). ARPEGE® 2.0 has enabled the creation of the module for the collection of electronic PROs in routine care for observational research and ultimately clinical care.

The content of ARPEGE® 2.0's initial electronic PROs module is based on current treatment guidelines for people being treated for HIV and associated comorbidities [4]. Prototyping was carried out over 2017 with the support and regular feedback from a working group comprising research staff, local stakeholders, and end users (clinician and patient representatives). The questionnaires were evaluated individually according to their psychometric properties, administration method and length. The following areas are covered by the electronic PRO module: socioeconomic status and individual social and material deprivation [12], multidimensional quality of life (WHOQOL-HIV BREF) [13] , treatment burden (Treatment Burden Questionnaire) [14], physical activity (The Short Version of the International Physical Activity Questionnaire), alcohol use and screening for at-risk drinking behavior (Alcohol Use Disorders Identification Test Consumption, Fast Alcohol Consumption Evaluation) [15], tobacco and nicotine use and screening for tobacco dependency (Fagerström), cannabis (Cannabis Abuse Screening Test) and drug use, and, finally, depression (Patient Health Questionnaire) [16]. Conditional branching was used where appropriate. The module also allows patients to report any other treatment-related issues in a free text field. Where applicable, the International Society for Pharmacoeconomics and Outcomes Research ePRO Task Force's recommendations on adapting paper-based instruments were followed, ensuring that data produced are equivalent or superior to those generated from paper-based administration methods [17].

Recruitment

Nielsen's recommendations which favour conducting several iterative studies, each with a small number of participants, were adopted [85]. In round one (May 2018), evaluators were employees of the Inserm UMR 1219 Bordeaux Population Health Research Center or affiliated with the project, referred to herein as "research staff". In round two (June 2018), a convenience sample of PLWH being cared for at the St André Bordeaux University Hospital was identified by clinical staff either prior to or during their routine visit.

Procedure

The evaluation procedure differed between round one and round two. However, for both rounds, oral consent was obtained. It was then explained that each study participant (evaluator) would be provided with a unique identifier, which would allow him/her to create a personal account and to access the questionnaires. Evaluators were shown the study-specific brochure where the number would be written on a detachable coupon (Multimedia Appendix 1). They were asked to complete 5 tasks: : (1) navigate between pages on the publicly available website and locate key information, (2) create a user account, (3) confirm their account, (4) initiate the electronic PRO assessment, and (5) complete the electronic PRO assessment. Whether or not each task was completed with ease, assistance or not was monitored and a score of 2-0 was attributed (2, the task was completed with ease, and 0, it was not completed). The highest possible score was therefore 10 and the lowest score was 0. Neither round 1 nor round 2 evaluators were compensated.

In round one, research staff were provided with instructions detailing the background of the study and how it would be implemented in a clinical setting. Evaluators were given a link to a staging version of the electronic PROs module. They were asked to complete the previously described tasks. They then responded to an online questionnaire that included the System Usability Scale (SUS), a widely used, robust tool for measuring usability. It consists of 10 items with five response options, from strongly agree to strongly disagree [90, 91]. Evaluators provided written feedback in an open text field and by email.

In round two, patients participated in one-on-one testing sessions, lasting between 1 and 2 hours, with a researcher in a dedicated, private space at the hospital (June, 2018). The researcher based each session on a standardized qualitative interview guide. A personal computer (Mac Book Air) with access to the staging site was provided to complete the study tasks. Patient evaluators were also allowed to complete the questionnaire on their personal Smartphones, matching how the electronic PROs module might be accessed in routine care. Evaluators were instructed to use the *think aloud* method, in which users are

asked to verbalize all thoughts as they interact with the system, while carrying out tasks. Subsequently, those who completed all tasks responded orally to the SUS and provided open-ended feedback [90]. All sessions were audio-recorded and field notes were taken.

Analysis

Task completion and SUS scores were calculated for each evaluator and means and standard deviations were calculated for each round. We performed a *t* test assuming unequal variance to determine if each round of testing produced significant difference in the mean SUS scores. A priori, we defined *success* in usability when the SUS reached a ceiling effect, with a minimum score of 70 – generally accepted as a cut-off for "good" usability [92].

Qualitative analysis included review of written feedback, audio recording-enhanced field notes, and responses to open-ended questions. We performed thematic-content analysis on written feedback and audio-recording enhanced field notes, abstracting and compiling emerging themes from each round of testing. These are reported according to the Nielsen's usability heuristic categories [83].

Results

Table 1 presents evaluators' characteristics and mean task completion scores for rounds 1 and 2. The majority of round 1 evaluators were women (7/8). They reported using computers either regularly (5/8) or often (3/8). Five out of seven round 2 evaluators were men. Three reported using a computer regularly, three often and one never. Overall, mean task completion scores were 7.8 (out of 10) in round 1 and 7.1 in round 2. In round 1, seven evaluators completed all tasks compared to four out of seven in round 2. Task completion was hampered due to 2 evaluators being locked out of their accounts and one evaluator being unable to complete tasks due to poor eyesight. This evaluator was attributed 0 on all tasks.

TABLE 1 : EVALUATOR CHARACTERISTICS AND TASK SCORES

Evaluator characteristics	Task 1	Task 2	Task 3	Task 4	Task 5	Total
	Information found	Account created	Account confirmed	PROs assessment initiated	PROs assessment completed	
Round 1 (N=8)	**2.0**	**1.1**	**1.4**	**1.5**	**1.8**	**7.8**
Male (n=1)	2.0	0.0	0.0	0.0	0.0	2.0
30-40	2.0	0.0	0.0	0.0	0.0	2.0
Female (n=7)	2.0	1.3	1.6	1.7	2.0	8.6
<30	2.0	1.5	1.5	1.5	2.0	8.5
30-40	2.0	1.3	1.3	1.7	2.0	8.3
41-50	2.0	1.0	2.0	2.0	2.0	9.0
>50	2.0	1.0	2.0	2.0	2.0	9.0
Round 2 (N=7)	**1.7**	**1.1**	**1.4**	**1.7**	**1.1**	**7.1**
Male (n=5)	1.6	1.2	1.6	1.6	1.6	7.6
<30	2.0	1.5	2.0	2.0	2.0	9.5
30-40	2.0	2.0	2.0	2.0	2.0	10.0
>50	1.0	0.5	1.0	1.0	1.0	4.5
Female (n=2)	2.0	1.0	1.0	2.0	0.0	6.0
>50	2.0	1.0	1.0	2.0	0.0	6.0

The usability insights uncovered during the two rounds of usability evaluations together with the solutions adopted are presented in Table 2.

TABLE 2 : USABILITY INSIGHTS PER ROUND AND SOLUTION ADOPTED ACCORDING TO THE NIELSEN'S USABILITY HEURISTICS

Usability categories	*Round 1—research staff*	*Round 2—patients*	*Solution*
Visibility of system status			
	Login procedure was confusing owing to the complexity of password, requiring 2 symbols	Challenges adhering to password requirements for certain patients	Password requirements were spelled out for users in bold. A password visualization button was also added to the password field to allow users to ensure that passwords created matched before registering their account
	—	Unclear whether the QuAliV number (required for creating the account) is case sensitive	Information incorporated into the presentation of the study to participants
	Validation of questionnaire unclear	—	Information buttons added to the home page of the electronic PRO[a] module instructing users on how the questionnaires functioned and reminding them to *submit* their completed questionnaires. The button was also relabeled to make its functionality clearer
Match between system and the real world			
	Date picker was in English and began in 2018, requiring users to click to go back in time	—	The date picker was replaced with a French version. It allowed users to type in their birth dates without using the calendar
	—	Nonmutually exclusive modalities or response missing	Minor modifications made to question modalities to ensure clarity
	—	Issues stemming from the translation of questionnaire from English to French	Further cognitive debriefing with native speakers to identify the best translation of the item in question
	—	Difficulties understanding the meaning of certain questions	Less formal language substituted where possible and examples given to facilitate the comprehension of certain questions
	—	Confirmation of account on one's smartphone (email) resulted in being locked out of one's account on another device	Automatic connection to the site after creating one's account deleted (temporarily) to avoid users locking themselves out of their account. Users must reenter their username and password
User control and freedom			
	Need for returning back to last page completed in the questionnaire	—	The user is now redirected back to the most recent page completed within each questionnaire. Scrolling from one page of a questionnaire to another automatically saves entered data
	Radio button could not be unclicked or erased	—	A refresh button was added to each item to allow users to erase their responses and therefore leave items unanswered
	Questionnaire opens in a pop-up window whose size cannot be modified	—	Double checked to ensure that text could be easily read in each window
	—	Unclear whether users had to provide first and last name	We added text indicating that typing one's first and last name was optional
Consistency and standards			
	Format of certain questions was noted as being inconsistent between questionnaires. Yes/No questions appeared in a table format as soon as they used the same response thesaurus	—	Minor improvements in formatting were made where possible. Further development required to accommodate this change in the longer run

	Typos in certain questions were identified	—	—
Error prevention			
	Aberrant response possible for certain free text fields	—	Stricter constraints added
	The password required was complex. Instructions on password requirements were missing from the account creation page	—	Instructions on password requirements added
	Need to clarify units in free text fields		Units added in gray in each text field
	Need to indicate which questions were mandatory in the questionnaire. Need to indicate when multiple answers could be given	—	An asterisk was added to indicate which questions were mandatory. The user is sent back to mandatory questions before being allowed to progress in the questionnaire. These questions were marked in red to indicate that they were mandatory
Recognition rather than recall	Automatic logout obligations meant that users could not reconnect to their accounts for 20 min if they left the page, resulting in certain evaluators being locked out of their account	—	Error message added to the module explaining that users would be able to reaccess their accounts after 20 min
Flexibility and efficiency of use			
	Errors encountered with the progress bar depending on responses to questions	—	Questionnaires are programmed to open successively
	Errors on certain Web browsers	—	Further trouble shooting using full array of browsers and devices
Aesthetic and minimalist design			
	Methods for completing a visual analog scale unclear as definition of extreme values was missing, and a *not applicable* box was not included	—	An 11-point radio button scale was proposed as a temporary solution
	The IPAQ[b] questionnaire was difficult to read on the pop-up screen	—	Alternative formatting used to improve readability
Help users with errors	Need to flag missed items	—	Progression bar for each questionnaire goes from orange to green as soon as all nonconditional questions are answered. Users are directed to unanswered obligatory questions upon attempting to go on to the next page of the questionnaire
Help and documentation			
	Information missing from different links (contact and preferences)	—	—
	Print button of informed non-opposition did not function correctly	—	—

a Not applicable.
b PRO: patient-reported outcome.
c IPAQ: International Physical Activity Questionnaire.

What Worked

The first task involved navigating the external website that patients would access from home, unassisted, to create their account. Users found the information provided on the external website quickly and found its structure clear. All users quickly understood how the attributed unique identifier would be used to create their personal account. Once users had created their account, efforts to guide him/her through electronic PROs by having each questionnaire open one after the other appeared to work well. The use of stoplight-style color coding and a progress bar allowed users to see if they had missed a question and helped them recognize, diagnose, and recover from errors seamlessly. The order of the PROs was received positively by users and therefore remained unchanged between prototype versions.

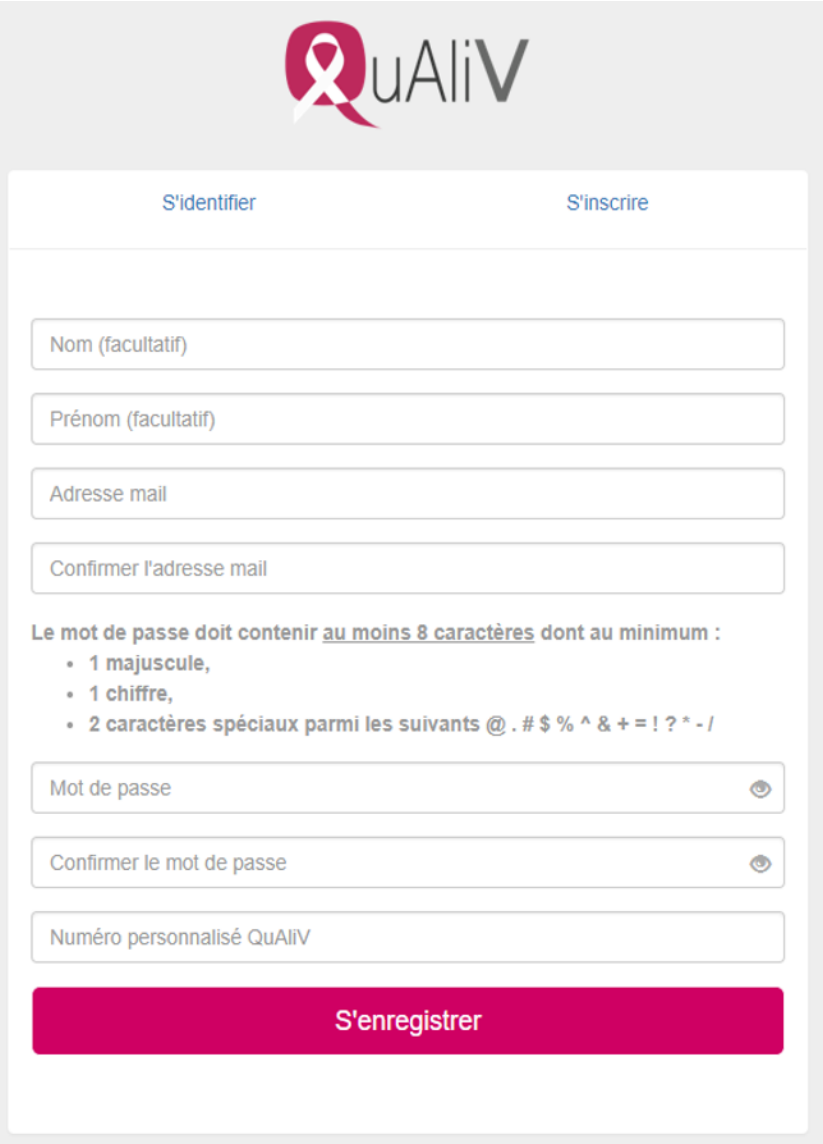
What Did Not Work

The account creation task was the most challenging for users. One of the issues identified was the complexity of the password requirements. The password had to be entered twice and contain at least 8 alphanumeric characters, including 2 special characters and a capital letter (Figure 4). Many evaluators, both research staff and patients, attempted this step more than once. We clarified the password requirements and ensured that error messages were informative regarding the system status and we made it possible to visualize the password after round one (Figure 5). As errors still occurred,

we added additional error prevention features. The password is validated as the user types as opposed to the user receiving an error message upon clicking “register” (Figure 6).

Fields (top to bottom) : Name, First Name, E-mail address, Confirm e-mail address, Password, Confirm password, QuAliV Number.
Password instructions (in bold): The password must contain at least 8 characters (letters and numbers) of which one must be uppercase and two special characters among the following @ . # $ ^ & + = ! ?

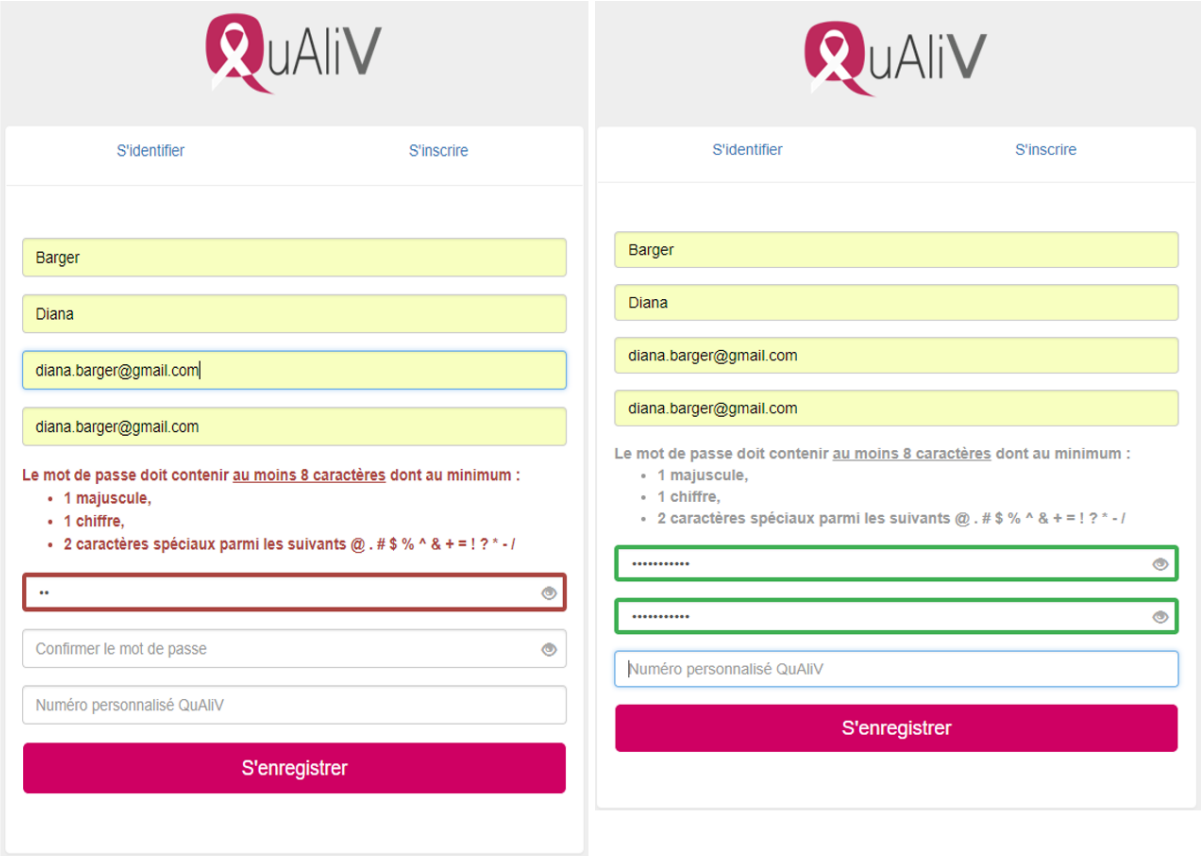
FIGURE 4 : INITIAL LOGIN PAGE (ROUND 1)



Fields (top to bottom) : Name (optional), First Name (optional), E-mail address, Confirm e-mail address, Password, Confirm password, QuAliV Number.

Password instructions (in bold): The password must contain at least 8 characters : 1 uppercase, 1 number and 2 special characters among the following @ . # $ ^ & + = ! ? * /

FIGURE 5 : REVISED LOGIN PAGE (ROUND 2)



Fields (top to bottom) : Name (optional), First Name (optional), E-mail address, Confirm e-mail address, Password, Confirm password, QuAliV Number.
Password instructions (in bold): The password must contain at least 8 characters : 1 uppercase, 1 number and 2 special characters among the following @ . # $ ^ & + = ! ? * /

FIGURE 6: ACCOUNT CREATION, PASSWORD CONTROLS

A login problem, also detected during the second round of usability testing, was being *locked out* of one's account accidentally. This issue arose from a security measure included in the electronic PRO module's design. Users were logged out automatically after a period of 20 min of inactivity. If users accidently left the page without logging out of their accounts, they could no longer log back in owing to the Bordeaux University servers' restrictions. If the user attempted to return to their account, they received an error message indicating that they were already connected. This issue could not be resolved without completely relaxing the automatic logout timeframe (shortening it). We therefore modified the error message indicating that the user could access their account again in 20 min.

System Usability Scales Scores

In round 1, experts reported mean SUS scores of 65 ± 18.87 and patients, in round 2, reported mean SUS scores of 85 ± 5.4 (p=0.032).

Discussion

Iterative usability evaluations of two successively developed prototypes allowed us to see how easy our electronic PROs module was to use and identify when and where users encountered problems or experienced confusion. We were able to improve the module's usability markedly, specifically the visibility of system status and the match between the system and the real world, and take into account the specific needs of our patient population (their level of computer literacy, age, etc.) and the specificities of our clinical setting. Finally, we were pushed to find the appropriate balance between optimal security and ease of use.

Unlike PROs collection methods employed in clinics in the United States [9, 10, 89], where patients complete an electronic PROs assessment using touchscreen information technology with the assistance of a research assistant/administrator at clinics, we aimed to design a web-based "Bring Your Own Device" solution. We therefore assumed that the majority of users would have access to a Smartphone or personal computer with reliable Internet. The proposed solution, developed in house, had to work well enough to allow a group of users, with varying levels of computer familiarity, to use it with little to no assistance.

Some caveats should be considered in the interpretation of our results. We conducted the first round of usability testing in a sample of research staff who may not fully represent end users. This strategy, recognized as an easy way of catching obvious usability issues, resulted in high quality, detail-oriented and exhaustive feedback, allowing for a number of basic usability problems to be resolved prior to evaluations with patients. Most evaluators were comfortable using computers and the Internet. They may not fully reflect the diversity of the cohort of PLWH in the region. More purposeful sampling of evaluators with lower computer literacy may have resulted in the detection of additional usability insights. In round 2, we used the "think aloud" method. This method has been known to slow the thought process and increase mindfulness, which might prevent errors that might have normally occurred [93]. But, when evaluators are asked to perform simple tasks, the method has been shown to have no effect on user performance [94]. We opted for this method as the tasks were not considered complex.

Nevertheless, software modifications, informed by successive rounds of usability testing, resulted in sufficient gains in usability to undertake piloting.

Funding

The Aquitaine ANRS Cohort is sponsored by the Bordeaux University Hospital and funded by the ANRS (France REcherche Nord&Sud Sida-hiv Hépatites), the Bordeaux University Hospital and the Inserm UMR 1219 - Bordeaux Population Health Research Centre. Seed funding was granted by the ANRS in 2017 via the CSS-5 call to develop the electronic PRO module. Diana Barger was awarded a 36-month “young researcher” grant from Sidaction to design and conduct a study on quality of life in people living with HIV within the ANRS CO3 Aquitaine cohort as part of her doctoral research.

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Conflicts of interest

DB has received a speaking fee from Gilead. FB declares to have received reimbursement for attending a symposium from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen, speaking fee and consultancy fee from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen, and funds for research from Gilead and ViiV Healthcare. The other authors do not have any conflict of interest to declare.

Original Paper

Web-Based Module for the Collection of Electronic Patient-Reported Outcomes in People Living With HIV in Nouvelle Aquitaine, France: Usability Evaluation

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Abstract

Background: Patient-reported outcomes (PROs) can be of great value for both research and chronic disease management. We developed a new module of the ANRS CO3 Aquitaine cohort study's Web-based data capture and visualization solution (APPEGE 2.0) for the collection of electronic PROs among people living with HIV cared for in Nouvelle Aquitaine, France.

Objective: This study aimed to evaluate the usability of 2 successively developed prototypes of ARPEGE 2.0's electronic PROs module before launching a pilot study, owing to the novelty of the proposed data collection method for our setting and specific characteristics of the target population.

Methods: A total of 2 sequential rounds of empirical, task-based usability evaluations were conducted, involving 8 research staff and then 7 people living with HIV. Evaluators provided written feedback during round 1 and oral feedback during round 2. Evaluators who completed the full set of tasks responded to the System Usability Scale (SUS). We assessed changes in SUS scores between rounds and concluded usability testing when SUS scores reached a ceiling effect, defining good usability a priori as a usability score of 70.

Results: Insights were generated regarding the visibility of system status and the match between the system and the real world that improved the module's usability. Research staff evaluators reported mean SUS scores of 65 (SD 18.87) and patient evaluators reported mean SUS scores of 85 (SD 5.4; P=.032).

Conclusions: Software modifications, informed by successive rounds of usability testing, resulted in sufficient gains in usability to undertake piloting. Insights generated during evaluations prompted us to find the appropriate balance between optimal security and ease of use.

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KEYWORDS

patient reported outcome measures; patient generated health data; quality of life

Introduction

HIV, once fatal, is now a manageable chronic illness [1]. In Western Europe, the majority of individuals who received a diagnosis of HIV are in care and on potent antiretroviral therapy, which prevents serious diseases both related and unrelated to AIDS [2]. The improved prognosis and the increased life expectancy of people living with HIV (PLWH) makes preserving health and ensuring good quality of life the cornerstone of their care [3-5]. One strategy to help providers respond to PLWH's evolving needs and improve the quality and efficiency of their overall care is collecting and using patient-reported outcomes (PROs) [6].

PROs or "any report of the status of the patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [7] have been used extensively in clinical research [6]. PROs can be used at the population level for research and to improve the quality of care or at the individual level to support clinical decision making [8]. Their use may allow for more accurate symptom detection, better patient-provider communication, and improved outcomes [9]. Logistical, technical, and ideological barriers have nevertheless limited their use in routine care [10]. The adoption of electronic medical records coupled with the adaptation of paper questionnaires to computerized and internet-based formats may help overcome these barriers [10,11].

With evidence from the United States suggesting that the collection of PROs by using touchscreen-based information technology was both feasible and of value for both research and clinical HIV care [12-14], a prototype of an electronic PRO module linked to the ANRS CO3 Aquitaine cohort's data capture and visualization system (ARPEGE 2.0) was developed in 2017 [15]. As the overall usefulness of interactive health care applications or their usability is likely to affect their acceptability and adoption, usability evaluations of 2 successively developed prototypes of the ARPEGE 2.0 solution were conducted in preparation for a pilot study [15].

Methods

This formative research study took place in Bordeaux, France, at the Inserm UMR 1219-Bordeaux Population Health Research Centre and the St André Bordeaux University Hospital. It was designed as part of the ANRS CO3 Aquitaine study, an open, prospective hospital-based cohort of PLWH in care in 13 clinics in southwestern France. A local institutional review board approved the study's protocol (Comité de Protection de Personnes Sud-Ouest et Outre-Mer III) on September 18, 2017.

Description of the Electronic Patient-Reported Outcome Module Powered by ARPEGE 2.0

ARPEGE 1.0 is a proprietary, secure, electronic case report form developed in Microsoft ASP.NET (WebForm). Data are stored within a Microsoft SQL Server 2014–based data management system. The ANRS CO3 Aquitaine cohort relies on ARPEGE 1.0 for data capture. Clinical data, extracted from both medical records and laboratory data, derived from the hospital's laboratory information management systems, have been collected systematically since 1987 and electronically via ARPEGE 1.0 since 2013 with the support of Clinical Research Associates. ARPEGE 2.0 is a generic Web-based data capture and visualization system also developed in Microsoft ASP.NET (WebForm). ARPEGE 2.0 has enabled the creation of the module for the collection of electronic PROs in routine care for observational research and, ultimately, clinical care.

The content of ARPEGE 2.0's initial electronic PRO module is based on current treatment guidelines for people being treated for HIV and associated comorbidities [16]. Prototyping was carried out over 2017 with the support and regular feedback from a working group comprising research staff, local stakeholders, and end users (clinicians and patient representatives). The questionnaires were evaluated individually according to their psychometric properties, administration method, and length. The following areas are covered by the electronic PRO module: socioeconomic status and individual social and material deprivation [17], multidimensional quality of life (WHOQOL-HIV BREF) [18], treatment burden (Treatment Burden Questionnaire) [19], physical activity (the Short Version of the International Physical Activity Questionnaire), alcohol use and screening for at-risk drinking behavior (Alcohol Use Disorders Identification Test Consumption, Fast Alcohol Consumption Evaluation) [20], tobacco and nicotine use and screening for tobacco dependency (Fagerström), cannabis (Cannabis Abuse Screening Test) and drug use, and, finally, depression (Patient Health Questionnaire) [21].

Conditional branching was used where appropriate. The module also allows patients to report any other treatment-related issues in a free text field. Where applicable, the International Society for Pharmacoeconomics and Outcomes Research ePRO Task Force's recommendations on adapting paper-based instruments were followed, ensuring that data produced are equivalent or superior to those generated from paper-based administration methods [22].

Recruitment

Nielsen's recommendations that favor conducting several iterative studies, each with a small number of participants, were adopted [23]. In round 1 (May 2018), evaluators were employees of the Inserm UMR 1219 Bordeaux Population Health Research Center or affiliated with the project, referred to herein as *research staff*. In round 2 (June 2018), a convenience sample of PLWH being cared for at the St André Bordeaux University Hospital was identified by clinical staff either before or during their routine visit.

Procedure

The evaluation procedure differed between round 1 and round 2. However, for both rounds, oral consent was obtained. It was

then explained that each study participant (evaluator) would be provided with a unique identifier, which would allow him/her to create a personal account and access the questionnaires. Evaluators were shown the study-specific brochure where the number would be written on a detachable coupon (Multimedia Appendix 1). They were asked to complete 5 tasks: (1) navigate between pages on the publicly available website and locate key information, (2) create a user account, (3) confirm their account, (4) initiate the electronic PRO assessment, and (5) complete the electronic PRO assessment. Whether or not each task was completed with ease, assistance or not was monitored, and a score of 2 to 0 was attributed (2=the task was completed with ease and 0=it was not completed). The highest possible score was therefore 10, and the lowest score was 0. Neither round 1 nor round 2 evaluators were compensated.

In round 1, research staff were provided with instructions detailing the background of the study and how it would be implemented in a clinical setting. Evaluators were given a link to a staging version of the electronic PRO module. They were asked to complete the previously described tasks. They then responded to an Web-based questionnaire that included the System Usability Scale (SUS), a widely used robust tool for measuring usability. It consists of 10 items with 5 response options, from strongly agree to strongly disagree [24,25]. Evaluators provided written feedback in an open text field and by email.

In round 2, patients participated in one-on-one testing sessions, lasting between 1 and 2 hours, with a researcher in a dedicated, private space at the hospital (June 2018). The researcher based each session on a standardized qualitative interview guide. A personal computer (Mac Book Air) with access to the staging site was provided to complete the study tasks. Patient evaluators were also allowed to complete the questionnaire on their personal smartphones, matching how the electronic PRO module might be accessed in routine care. Evaluators were instructed to use the *think aloud* method, in which users are asked to verbalize all thoughts as they interact with the system while carrying out tasks. Subsequently, those who completed all tasks responded orally to the SUS and provided open-ended feedback [24]. All sessions were audio recorded, and field notes were taken.

Analysis

Task completion and SUS scores were calculated for each evaluator, and means and standard deviations were calculated for each round. We performed a *t* test assuming unequal variance to determine if each round of testing produced significant difference in the mean SUS scores. A priori, we defined *success* in usability when the SUS score reached a ceiling effect, with a minimum score of 70—generally accepted as a cut-off for *good* usability [26].

Qualitative analysis included review of written feedback, audio recording–enhanced field notes, and responses to open-ended questions. We performed thematic content analysis on written feedback and audio recording–enhanced field notes, abstracting and compiling emerging themes from each round of testing. These are reported according to Nielsen's usability heuristic categories [27].

Results

Overview

Table 1 presents evaluators' characteristics and mean task completion scores for rounds 1 and 2. The majority of round 1 evaluators were women (7/8). They reported using computers either regularly (5/8) or often (3/8). In all, 5 out of 7 round 2 evaluators were men. A total of 3 reported using a computer regularly, 3 often, and 1 never. Overall, mean task completion scores were 7.8 (out of 10) in round 1 and 7.1 in round 2. In round 1, 7 evaluators completed all tasks compared with 4 out of 7 in round 2. Task completion was hampered owing to 2 evaluators being locked out of their accounts and 1 evaluator being unable to complete tasks owing to poor eyesight. This evaluator was attributed 0 on all tasks.

The usability insights uncovered during the 2 rounds of usability evaluations together with the solutions adopted are presented in Table 2.

Table 1. Evaluator characteristics and task scores.

Evaluator characteristics	Task 1—information found	Task 2—account created	Task 3—account confirmed	Task 4—PRO[a] assessment initiated	Task 5—PRO assessment completed	Total
Round 1 (N=8)	2.0	1.1	1.4	1.5	1.8	7.8
Male (n=1)	2.0	0.0	0.0	0.0	0.0	2.0
30-40	2.0	0.0	0.0	0.0	0.0	2.0
Female (n=7)	2.0	1.3	1.6	1.7	2.0	8.6
<30	2.0	1.5	1.5	1.5	2.0	8.5
30-40	2.0	1.3	1.3	1.7	2.0	8.3
41-50	2.0	1.0	2.0	2.0	2.0	9.0
>50	2.0	1.0	2.0	2.0	2.0	9.0
Round 2 (N=7)	1.7	1.1	1.4	1.7	1.1	7.1
Male (n=5)	1.6	1.2	1.6	1.6	1.6	7.6
<30	2.0	1.5	2.0	2.0	2.0	9.5
30-40	2.0	2.0	2.0	2.0	2.0	10.0
>50	1.0	0.5	1.0	1.0	1.0	4.5
Female (n=2)	2.0	1.0	1.0	2.0	0.0	6.0
>50	2.0	1.0	1.0	2.0	0.0	6.0

[a]PRO: patient-reported outcome.

Table 2. Usability insights per round and solution adopted according to Nielsen's usability heuristics.

Usability categories	Round 1—research staff	Round 2—patients	Solution
Visibility of system status	Login procedure was confusing owing to the complexity of password, requiring 2 symbols	Challenges adhering to password requirements for certain patients	Password requirements were spelled out for users in bold. A password visualization button was also added to the password field to allow users to ensure that passwords created matched before registering their account
	__[a]	Unclear whether the QuAliV number (required for creating the account) is case sensitive	Information incorporated into the presentation of the study to participants
	Validation of questionnaire unclear	—	Information buttons added to the home page of the electronic PRO[b] module instructing users on how the questionnaires functioned and reminding them to *submit* their completed questionnaires. The button was also relabeled to make its functionality clearer
Match between system and the real world	Date picker was in English and began in 2018, requiring users to click to go back in time	—	The date picker was replaced with a French version. It allowed users to type in their birth dates without using the calendar
	—	Nonmutually exclusive modalities or response missing	Minor modifications made to question modalities to ensure clarity
	—	Issues stemming from the translation of questionnaire from English to French	Further cognitive debriefing with native speakers to identify the best translation of the item in question
	—	Difficulties understanding the meaning of certain questions	Less formal language substituted where possible and examples given to facilitate the comprehension of certain questions
	—	Confirmation of account on one's smartphone (email) resulted in being locked out of one's account on another device	Automatic connection to the site after creating one's account deleted (temporarily) to avoid users locking themselves out of their account. Users must reenter their username and password
User control and freedom	Need for returning back to last page completed in the questionnaire	—	The user is now redirected back to the most recent page completed within each questionnaire. Scrolling from one page of a questionnaire to another automatically saves entered data
	Radio button could not be unclicked or erased	—	A refresh button was added to each item to allow users to erase their responses and therefore leave items unanswered
	Questionnaire opens in a pop-up window whose size cannot be modified	—	Double checked to ensure that text could be easily read in each window
	—	Unclear whether users had to provide first and last name	We added text indicating that typing one's first and last name was optional
Consistency and standards	Format of certain questions was noted as being inconsistent between questionnaires. Yes/No questions appeared in a table format as soon as they used the same response thesaurus	—	Minor improvements in formatting were made where possible. Further development required to accommodate this change in the longer run
	Typos in certain questions were identified	—	—
Error prevention	Aberrant response possible for certain free text fields	—	Stricter constraints added
	The password required was complex. Instructions on password requirements were missing from the account creation page	—	Instructions on password requirements added
	Need to clarify units in free text fields		Units added in gray in each text field

Usability categories	Round 1—research staff	Round 2—patients	Solution
	Need to indicate which questions were mandatory in the questionnaire. Need to indicate when multiple answers could be given	—	An asterisk was added to indicate which questions were mandatory. The user is sent back to mandatory questions before being allowed to progress in the questionnaire. These questions were marked in red to indicate that they were mandatory
Recognition rather than recall	Automatic logout obligations meant that users could not reconnect to their accounts for 20 min if they left the page, resulting in certain evaluators being locked out of their account	—	Error message added to the module explaining that users would be able to reaccess their accounts after 20 min
Flexibility and efficiency of use	Errors encountered with the progress bar depending on responses to questions	—	Questionnaires are programmed to open successively
	Errors on certain Web browsers	—	Further trouble shooting using full array of browsers and devices
Aesthetic and minimalist design	Methods for completing a visual analog scale unclear as definition of extreme values was missing, and a *not applicable* box was not included	—	An 11-point radio button scale was proposed as a temporary solution
	The IPAQ[c] questionnaire was difficult to read on the pop-up screen	—	Alternative formatting used to improve readability
Help users with errors	Need to flag missed items	—	Progression bar for each questionnaire goes from orange to green as soon as all nonconditional questions are answered. Users are directed to unanswered obligatory questions upon attempting to go on to the next page of the questionnaire
Help and documentation	Information missing from different links (contact and preferences)	—	—
	Print button of informed nonopposition did not function correctly	—	—

[a]Not applicable.

[b]PRO: patient-reported outcome.

[c]IPAQ: International Physical Activity Questionnaire.

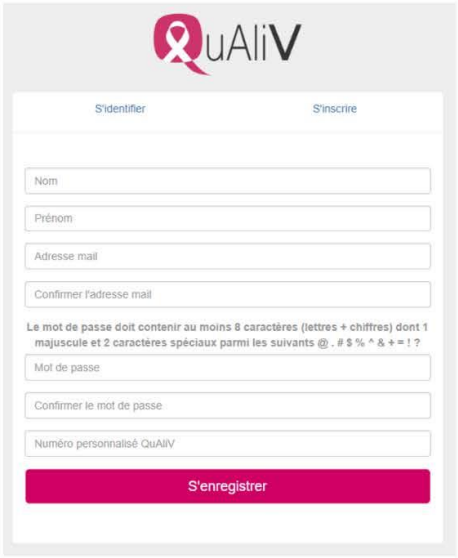
What Worked

The first task involved navigating the external website that patients would access from home, unassisted, to create their account. Users found the information provided on the external website quickly and found its structure clear. All users quickly understood how the attributed unique identifier would be used to create their personal account. Once users had created their account, efforts to guide him/her through electronic PROs by having each questionnaire open one after the other appeared to work well. The use of stoplight-style color coding and a progress bar allowed users to see if they had missed a question and helped them recognize, diagnose, and recover from errors seamlessly. The order of the PROs was received positively by users and therefore remained unchanged between prototype versions.

What Did Not Work

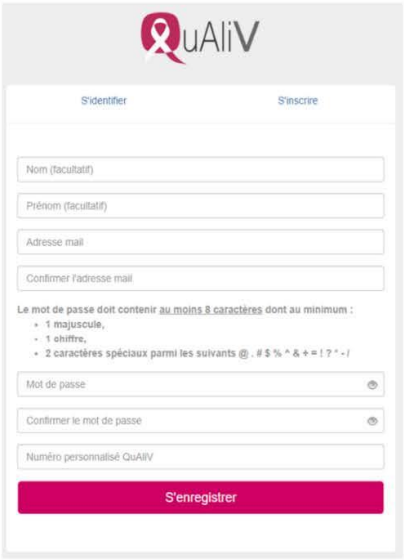
The account creation task was the most challenging for users. One of the issues identified was the complexity of the password requirements. The password had to be entered twice and contain at least 8 alphanumeric characters, including 2 special characters and a capital letter (Figure 1). Many evaluators, both research staff and patients, attempted this step more than once. We clarified the password requirements and ensured that error messages were informative regarding the system status, and we made it possible to visualize the password after round 1 (Figure 2). As errors still occurred, we added additional error prevention features. The password is validated as the user types as opposed to the user receiving an error message upon clicking *register* (Multimedia Appendix 2).

Figure 1. Initial log-in page (round 1).



Fields (top to bottom) : Name, First Name, E-mail address, Confirm e-mail address, Password, Confirm password, QuAliV Number.
Password instructions (in bold): The password must contain at least 8 characters (letters and numbers) of which one must be uppercase and two special characters among the following @ . # $ ^ & + = ! ?

Figure 2. Revised log-in page (round 2).



Fields (top to bottom) : Name (optional), First Name (optional), E-mail address, Confirm e-mail address, Password, Confirm password, QuAliV Number.
Password instructions (in bold): The password must contain at least 8 characters : 1 uppercase, 1 number and 2 special characters among the following @ . # $ ^ & + = ! ? * /

A login problem, also detected during the second round of usability testing, was being *locked out* of one's account accidentally. This issue arose from a security measure included in the electronic PRO module's design. Users were logged out automatically after a period of 20 min of inactivity. If users accidently left the page without logging out of their accounts, they could no longer log back in owing to the Bordeaux University servers' restrictions. If the user attempted to return to their account, they received an error message indicating that they were already connected. This issue could not be resolved without completely relaxing the automatic logout timeframe (shortening it). We therefore modified the error message indicating that the user could access their account again in 20 min.

System Usability Scale Scores

In round 1, experts reported mean SUS scores of 65 (SD 18.87), and patients, in round 2, reported mean SUS scores of 85 (SD 5.4) (P=.032).

Discussion

Principal Findings

Iterative usability evaluations of 2 successively developed prototypes allowed us to see how easy our electronic PRO module was to use and identify when and where users encountered problems or experienced confusion. We were able to improve the module's usability markedly, specifically the visibility of system status and the match between the system and the real world, and take into account the specific needs of our patient population (their level of computer literacy and age) and the specificities of our clinical setting. Finally, we were pushed to find the appropriate balance between optimal security and ease of use.

Unlike PRO collection methods employed in clinics in the United States [12-14], where patients complete an electronic PRO assessment by using touchscreen information technology with the assistance of a research assistant/administrator at clinics, we aimed to design a Web-based *Bring Your Own Device* solution. We therefore assumed that the majority of users would have access to a smartphone or personal computer with a reliable internet connection. The proposed solution, developed in-house, had to work well enough to allow a group of users, with varying levels of computer familiarity, to use it with little to no assistance.

Strengths and Limitations

Some caveats should be considered in the interpretation of our results. We conducted the first round of usability testing in a sample of research staff who may not fully represent end users. This strategy, recognized as an easy way of catching obvious usability issues, resulted in high-quality, detail-oriented, and exhaustive feedback, allowing for a number of basic usability problems to be resolved before evaluations with patients. Most evaluators were comfortable using computers and the internet. They may not fully reflect the diversity of the cohort of PLWH in the region. More purposeful sampling of evaluators with lower computer literacy may have resulted in the detection of additional usability insights.

In round 2, we used the *think aloud* method. This method has been known to slow the thought process and increase mindfulness, which might prevent errors that might have normally occurred [28]. However, when evaluators are asked to perform simple tasks, the method has been shown to have no effect on user performance [29]. We opted for this method as the tasks were not considered complex.

Conclusions

Nevertheless, software modifications, informed by successive rounds of usability testing, resulted in sufficient gains in usability to undertake piloting.

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Conflicts of Interest

DB has received a speaking fee from Gilead. FB declares to have received reimbursement for attending a symposium from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen, speaking fee and consultancy fee from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen, and funds for research from Gilead and ViiV Healthcare. The other authors do not have any conflict of interest to declare.

Multimedia Appendix 1

Patient brochure with unique identifier.
[PNG File , 478 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Login page with password verification.
[PNG File , 234 KB-Multimedia Appendix 2]

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Abbreviations

PLWH: people living with HIV
PRO: patient-reported outcome
SUS: System Usability Scale

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Chapter 3: Acceptability

Introduction & Aims

As logistical barriers have impeded the collection of PROs in our setting and elsewhere, we evaluated initial acceptability of an electronic PROs (ePROs) IT system linked to the ANRS CO3 Aquitaine cohort's data capture system (ARPEGE® 2.0). We aimed to (1) describe the socio-demographic, epidemiological and clinical characteristics of participants according to their level of engagement in the QuAliV ancillary study (definitions below). We then sought to investigate the presence of potential selection biases related to (a) CRA/investigators, (b) ineligibility due to French language proficiency or neuropsychological problems, (c) refusal (d) non-response. Finally, we examined factors associated with "active participation" among people who are considered eligible for the ePROs module according to sex.

Methods

Study design

The ANRS CO3 Aquitaine cohort is an open, prospective, hospital-based cohort of adults (≥18 years old), with a confirmed HIV-1 diagnosis (Western Blot or ELISA), followed-up in 13 public hospital in the Nouvelle Aquitaine region of France, launched in 1987. Its current iteration "AQUIVIH", sponsored by the University Hospital of Bordeaux, aims to enrol most of the ANRS CO3 Aquitaine cohort's participants. A team of trained and highly experienced CRAs abstracts clinical and biological data from patients' paper or electronic medical record. Data are entered in a web-based electronic Case Report Form (ARPEGE 1.0). The "QuAliV" study was designed as a novel ancillary study within the current iteration of the ANRS CO3 Aquitaine cohort, "AQUIVIH". Enrolment in the AQUIVIH cohort coincided with the QuAliV study, described in greater detail elsewhere [11].

In its current form, the QuAliV study is a cross-sectional study that aims to better capture PROs, including HRQoL, in a population of PLWH in care in 13 services in south-western France. It is novel because a new ePRO module linked to the cohort's data capture and visualisation system (ARPEGE 2.0) was designed and developed for this study and its usability evaluated prior to implementation [95]. To participate via the ePRO module version 1.0, participants had to have a personal e-mail account and a reliable Internet connection (basic requirements). For those who met the eligibility criteria but did not meet the basic requirements for the ePRO module, a paper version of questionnaires was made available. Participants who were cognitively impaired or could not read French well enough to complete a self-administered questionnaire were considered ineligible. CRA and investigators completed a study-

specific support document comprising information regarding recruitment to the ancillary study, specifically: the date of hospital consultation, the provision of information by the investigator, eligibility for the ePRO module or not, the status vis-à-vis his/her interest in the study at the end of the consultation (acceptance, ineligibility, and refusal) (Annex I).

Data sources and management

These analyses were based on three different data sources (i) the ANRS CO3 Aquitaine Cohort's database, (ii) data collected via the study-specific support document regarding recruitment, and (iii) metadata, extracted from ARPEGE 2.0's dashboard, comprised the unique identifier, date of registration, completeness of questionnaires and finally, whether or not the account was locked, and if so, the date the account was locked. These three data sources were merged.

We derived the participant's age, transmission route, coded as men who have sex with men (MSM), heterosexual, intravenous drug use, or other, county/region of origin (France, Europe, North/Sub Saharan Africa, Americas, Asia etc.), time in years since HIV diagnosis, time in years since start of first antiretroviral treatment, and HIV stage according to CDC categories. Participants' most recent CD4 T counts (cells/mm3) and viral load (copies/mL) were considered if they were collected within three-year window of the last consultation. CD4 T cell counts were categorised according to the following thresholds <200, 200-499, and ≥500 cells/mm. Viral load measures are presented according to the following thresholds <50, 50-200, ≥200 copies/mL and as the proportion of patients with a viral load <50 copies/mL. As the majority of the cohort participants are stable on ART, we also assessed an additional measure of overall health status, the presence or absence of additional comorbidities (chronic renal failure, cardiovascular event, hypertension (taking anti-hypertensive therapy), diabetes, cancer). Finally, it was also hypothesised that those with recent anxiety or depression (diagnosed within one year) might be less likely to registered and complete ePRO assessments.

Definitions of study population(s)

This analysis was performed in six different study populations:

(1) **Source population** : The "source population" or that which we wished to draw inferences about was restricted to those in care in open centres (N° 1, 2, 3, 3, 4, 5, 6, 24, 25, 90, 95) who had signed the consent of the ANRS CO3 cohort (or awaiting signature), were not deceased, and had at least one consultation or hospitalisation recorded between 01/01/2017 and the date of the extraction : 6 June 2019.

(2) **Theoretically eligible population**: Theoretic eligibility was defined as those for whom consent in the "AQUIVIH" had been provided and study documents had been prepared by the TECs and for whom, investigators had proposed the study during their hospital-based consultation. They were considered theoretically eligible if they presented for care between 23/7/2018 and 15/5/2019 in one of the open centres3. They were considered for this analysis if they had at least one recorded hospital consultation or had been hospitalisation between the 1st of January 2017 and the 6th of June 2019.

(3) **Truly eligible**: Those who were considered "truly eligible" were those invited to participate in the QuAliV ancillary study minus those who were perceived as ineligible by the investigator.

(4) **Recruited:** Patients in open centres who had the information, were solicited and accepted the study (Truly eligible participants minus refusals), stratified according to participation mode.

(5) **ePRO respondents :** Participants who were recruited and registered for the study from home as of the 4th of June.

(6) **paper-PROs respondents**: Participants who were recruited and completed a paper questionnaire and returned it as of the 4th of June.

Outcome of interest

To assess acceptability, the main outcome measures were having accepted to participate in the QuAliV ancillary study during the defined study period: 23 July 2019 – 15 May 2019. The secondary outcome measure was having registered to participate in the QuAliV ancillary study via the ePRO module. We defined participation as having been issued a QuAliV number upon receiving information about the ancillary study at the consultation. We defined "registration" (among those who agreed to participate and met the eligibility criteria for the ePRO module) as having created one's account independently by 4 June, 2019.

[3] open centres (N° 1, 2, 3, 4, 5, 6, 6, 24, 25, 90, 95)

Statistical Analysis

We undertook the statistical analysis using STATA version 15.1 (StatCorp LLC). We describe the initial recruitment and enrolment in this study, ongoing since July 2018. These results cover the initial 10-months of the study's implementation, from the 23rd of July 2018 to the 15th of May 2019, in five centres in south-western France (Bordeaux (n=3), Bayonne (n=1), Périgueux (n=1)). We present descriptive statistics according to pre-defined explanatory variables that were available for participants actively followed and present these stratified by different level of engagement. We present frequencies and proportions for categorical variables and means and standard deviations for continuous variables.

As the participants' sex was highly correlated with their age, transmission route category and country/region of birth, we performed restricted analyses by sex for each outcome of interest (participation, registration). We conducted bivariate analyses comparing age (in years), transmission route category and country/region of birth, CD4 T cell count thresholds, viral load thresholds, CDC stage, comorbidities (yes, no), time since diagnosis (years), time on treatment (years), and previous depression diagnosis. We used Chi-squared tests to compare categorical variables or the Fisher's exact test in cases where there were fewer than five observations and the T-Test or its non-parametric counterpart, the Mann Whitney test, to compare continuous variables.

Results

1,752 theoretically eligible participants were seen during the study period (23 July 2018 – 15 May 2019) and had not created their account or returned a paper questionnaire to the service by the 4th of June 2019. Twenty observations were excluded because of delays in data entry or lack of follow-up. We provide an overview of enrolment in the QuAliV ancillary study from between July 23rd, 2019 - May 15th, 2019 in Figure 7.

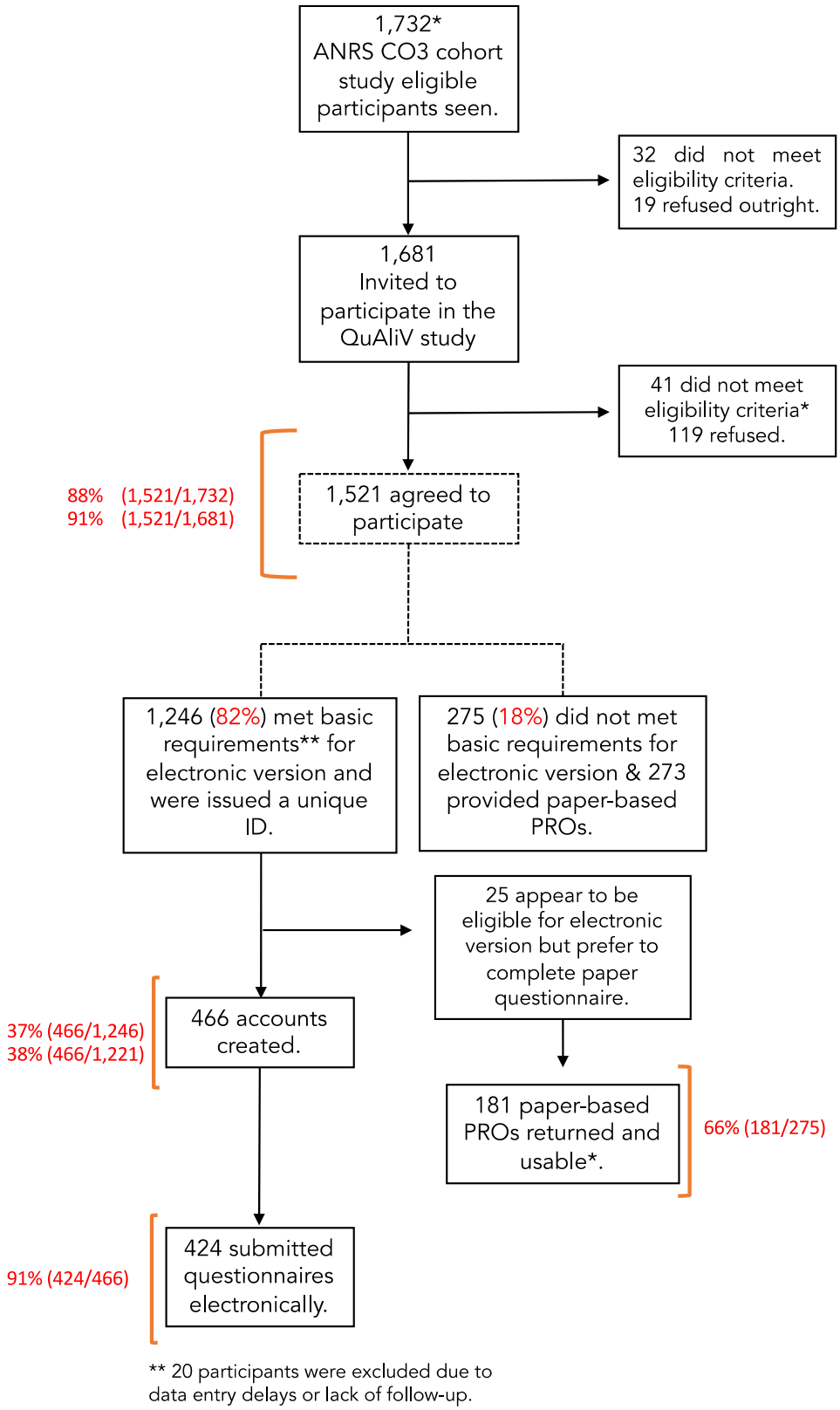

FIGURE 7 : FLOW CHART DURING THE INITIAL 10-MONTHS OF STUDY IMPLEMENTATION (23.7.2018 – 15.5.2019)

Among those who were theoretically eligible, 97.1% (1,681/1,732) received information and were invited to participated in the study. Fifty-one were either not invited to participate because they were considered to be ineligible by the investigator (n=32) or refused outright (n=19). Among those who were invited to participate, 90.5% (1,521/1,681) accepted, 7.1% (119/1,681) refused and an additional 2.4% (41/1,681) were ineligible. The majority of participants who refused did not provide a justification (55%, 66/121). The main reasons given were either disinterest (31%, 37/121) or lack of time (15% 18/121). Among for whom a reason for ineligibility was provided or 63% (57/90), 38.9% (35/90) did not speak and/or read French at all or well-enough to participate. The next reason provided was neurological or psychological impairment, accounting for 23% (22/90).

Table 3 provides a comparison of participants who accepted, declined or were ineligible according to socio-demographic and clinical characteristics. Among those who were considered ineligible, they were more often non-MSM and unsurprisingly foreign. They also appear to have poorer immunological and virological status compared to those who accepted. Nevertheless, there were no differences observed between groups in terms of their sex or age.

TABLE 3 : SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS ACCORDING TO PARTICIPATION STATUS (N=1732*)

	Accepted		Ineligible		Refused		Total		Chi2 / F Statistic	p-value
	N	% or $\bar{x}$(s)	N	% or $\bar{x}$(s)	N	% or $\bar{x}$(s)	N	% or $\bar{x}$(s)		
Gender										
Male	1133	74.5	61	67.8	85	70.3	1283	73.9	3.05	0.55 **
Female	387	25.4	29	32.2	36	29.8	452	26.0		
Transgender	1	0.1	-	-	-	-	1	0.06		
Age										
<30	40	2.6	2	2.2	4	3.3	46	2.7	4.05	0.853 **
30-39	174	11.5	12	13.3	13	10.7	200	11.5		
40-49	312	20.5	18	20.0	19	15.7	349	20.2		
50-59	579	38.1	37	41.1	45	37.2	663	38.2		
≧ 60	416	27.4	21	23.3	40	33.1	478	27.5		
Transmission route										
MSM	757	49.8	13	14.4	36	29.75	806	46.6	61.65	<0.001 **
Heterosexual	499	32.8	45	50.0	52	42.98	596	34.33		
IV Drug Use	162	10.7	22	24.4	19	15.7	203	11.75		
Other	103	6.8	10	11.1	14	11.57	127	7.35		
Country of origin										
France	1284	84.4	49	54.4	96	79.34	1429	82.5	57.75	<0.001 **
Europe	34	2.2	6	6.7	5	4.13	45	2.6		
N/SSA Africa	171	11.2	28	31.1	19	15.7	218	12.6		
Americas, Ocean	32	2.1	7	7.8	1	0.83	40	2.3		
Last CD4 T cell count (cells/ml)										
≧ 500	1080	71.0	44	48.9	79	65.3	1203	69.5	29.38	<0.001 **
200 – 499	326	21.4	37	41.1	31	25.6	394	22.7		
< 200	33	2.2	6	6.7	3	2.5	42	2.4		
Missing	82	5.4	3	3.3	8	6.6	93	5.4		
Last viral load (copies/mL)										
<50	1389	95.0	77	85.6	99	81.82	1565	90.4	22.86	0.001 **
50-199	51	3.5	7	7.8	6	4.96	64	3.7		
>200	22	1.5	4	4.4	5	4.13	31	1.8		
Missing	59	3.9	2	2.2	11	9.09	72	4.2		
Time since diagnosis (years)	1521	18.5 (9.8)	90	17.9 (10.3)	121	18.8 (10.0)	1732	18.5 (9.8)	0.21	0.811 †
Total exposure to ART (years)	1516	14.0 (7.6)	90	13.3 (8.5)	121	14.5 (8.2)	1731	14.0 (7.7)	0.53	0.587 †

* 1752 participants were seen between 23.07.2018 - 05.15.2019, account created or paper questionnaire submitted by 6.4.2019 ; 1732 considered for analysis

** results of the Chi2 analysis / † results of ANOVA

Among those who accepted, 82% (1,246/1,521) were considered to have met the basic requirements for the ePROs module whereas 18% (275/1,521) lacked either a personal e-mail address or a reliable Internet connection and 273 were provided with an identical paper questionnaire. Certain participants who met the basic requirements of the ePROs module subsequently requested a paper questionnaire (n=25). Among those who accepted and met the basic requirements for the ePROs module, 37.4% (466/1,246) registered as of 4 June 2019. Of those provided with a paper questionnaire, 68.9% (188/273) had returned these by the same date and 66.3% (181/273) of those who had returned them were of sufficiently completeness and legible enough to be entered. Among the 466 who created their accounts, 65% (305/466) did so within 1 week of the consultation and 88.2% (411/466) did so within 1 month of the consultation. Of those who created their account, 425 submitted their questionnaire and 362 did so within 1 month of its creation. Among those who registered, 44 had not begun the questionnaires.

As can be expected, those who met the basic requirements of the ePRO module compared to those who did not were quite different. Table 4 describes some of the characteristics of these two population. Those who did not meet the basic requirements for the ePROs module were more often older, women, and of African descent. They had more often acquired HIV from heterosexual contact compared to other transmission routes. In spite of these differences, groups had similar clinical characteristics. 68.7% of those who did not meet the basic requirements of the ePROs module had a CD4 T cell count above 500 cells/ml with the last three years of the consultation compared to 71.5% who did (p= 0.136). Similarly, 90.6% of those who did not meet the basic requirements had an undetectable viral load compared to 91.5% who did (p= 0.066).

TABLE 4 : ELIGIBILITY FOR E-PRO MODULE AMONG THOSE WHO ACCEPTED.

	Did not meet basic requirement for ePRO module (N= 277)		Met basic requirement for ePRO module (N= 1,260)		Total		Chi2 T-statistic	p-value
	N	% or $\bar{x}$ (s)	N	% or $\bar{x}$ (s)	N	% or $\bar{x}$ (s)		
Gender								
Male	165	60.0	968	77.7	1,133	74.5	37.64	<0.001**
Female	110	40.0	277	22.2	387	25.4		
Transgender	0	0.0	1	0.1	1	0.1		
Age								
<30	0	0.0	40	3.2	40	2.6	72.28	<0.001**
30-39	17	6.2	157	12.6	174	11.4		
40-49	41	14.9	271	21.8	312	20.5		
50-59	88	32.0	491	39.4	579	38.1		
≧ 60	129	46.9	287	23.0	416	27.4		
Transmission route								
MSM	81	29.5	676	54.3	757	49.8	55.98	<0.001**
Heterosexual	130	47.3	369	29.6	499	32.8		
IV Drug Use	38	13.8	124	10.0	162	10.7		
Other	26	9.5	77	6.2	103	6.8		
Country of origin								
France	201	73.1	1,083	86.9	1,284	84.4	52.61	<0.001
Europe	6	2.2	28	2.3	34	2.2		
N/SSA Africa	65	23.6	106	8.5	171	11.2		
Americas, Ocean	3	1.1	29	2.3	32	2.1		
Last CD4 cell count (cells/ml)								
≧ 500	189	68.7	891	71.5	1,080	71.0	5.54	0.136
200 – 499	65	23.6	261	21.0	326	21.4		
< 200	10	3.6	23	1.9	33	2.2		
Missing	11	4.0	71	5.7	82	5.4		
Last viral load (copies/mL)								
<50	249	90.6	1,140	91.5	1,389	91.3	7.21	0.066
50-199	13	4.7	38	3.1	51	3.4		
>200	7	2.6	15	1.2	22	1.5		
Missing	6	2.2	53	4.3	59	3.9		
Time since diagnosis (years)	275	19.8 (9.4)	1246	18.2 (9.8)	1521	18.5 (9.7)	2.39	0.017
Total exposure to ART (years)	275	15.1 (7.3)	1241	13.8 (7.7)	1516	14.0 (7.6)	2.61	0.009

** results of the Chi2 analysis / † results of Student's *t*-test

Men were slightly more likely than women to participate, however, this difference was not found to be statistically significant. The factors associated with participation differed by sex. In men, transmission route, place of origin, immunological and virological status were associated with participation. Those with a diagnosis of depression were also less likely to participate (Table 5). In women, participation was associated with place/region of origin and immunological status. Those who agreed were more often of French descent (Table 6). Statistically significant differences were also observed according to time since diagnosis and exposure to ART (which were highly correlated). Those who had been diagnosed for longer were more likely to participate.

TABLE 5 : FACTORS ASSOCIATED WITH PARTICIPATION RESTRICTED TO MEN

	Overall				Declined or ineligible				Agreed to participate				p-value
					N	%			N	%			
Age (median 25th and 75th percentile)	1279	54.8	46.9	61.5	146	55.4	47.9	61.1	1133	54.7	46.8	61.5	0.330†
Transmission route													
MSM	805	62.9			49	33.6			756	66.7			**<0.001****
Heterosexual	246	19.5			45	30.8			204	18.0			
IV Drug	143	11.2			35	24.0			108	9.5			
Other	82	6.4			17	11.6			65	5.7			
Place of origin													
France	1145	89.5			115	78.8			1030	90.9			**<0.001****
Europe	35	2.7			7	4.8			28	2.5			
N/SSA Africa	73	5.7			19	13.0			54	4.8			
Americas, Asia etc.	26	2.0			5	3.4			21	1.9			
Last CD4 cell count (cells/ml)													
≧ 500	895	70.0			87	59.6			808	71.3			**0.008****
200 – 499	290	22.7			45	30.8			245	21.6			
< 200	30	2.3			6	4.1			24	2.1			
Missing	64	5.0			8	5.5			56	4.9			
Last viral load (copies/mL)													
<50	1153	90.1			117	80.1			1036	91.4			**<0.001****
50-199	56	4.4			11	7.5			45	4.0			
>200	21	1.6			7	4.8			14	1.2			
Missing	49	3.8			11	7.5			38	3.4			
Time since diagnosis (years)	1279	19.1	9.6	9.6	146	20.3	12.7	28.3	1133	18.8	9.5	26.7	0.147†
Total exposure to ART (years)	1274	14.2	7.2	21.1	146	16.3	7.6	21.5	1128	13.8	7.2	21.0	0.217†
CDC Category													
A	767	60.0			77	52.7			690	60.9			0.115**
B	253	19.8			31	21.2			222	19.6			
C	259	20.3			38	26.0			221	19.5			
Comorbidities													
No	600	46.9			60	41.1			540	47.7			0.640**
Yes	613	47.9			77	52.7			536	47.3			
Missing	66	5.2			9	6.2			57	5.0			
Depression													
No	1124	88.0			120	82.2			1004	88.6			**0.025****
Yes	155	12.1			26	17.8			129	11.4			

** results of the Chi2 analysis / † results of Student's *t*-test

TABLE 6 : FACTORS ASSOCIATED WITH PARTICIPATION RESTRICTED TO WOMEN

	Overall				Declined or ineligible				Participation				
	N	%			N	%			N	%			p-values
Age (median 25th and 75th percentile)	452	52.8	44.4	59.2	65.0	53.2	45.0	64.3	387	52.8	44.3	58.8	0.662
Transmission route													
Heterosexual	347	76.8			52	80.0			295	76.2			0.580
IV Drug	60	13.3			6	9.2			54	14.0			
Other	45	10.0			7	10.8			38	9.8			
Place of origin													
France	283	62.6			30	46.2			253	65.4			0.006
Europe	10	2.2			4	6.2			6	1.6			
N/SSA Africa	145	32.1			28	43.1			117	30.2			
Americas, Asia etc.	14	3.1			3	4.6			11	2.8			
Last CD4 cell count (cells/ml)													
≧ 500	307	67.9			36	55.4			271	70.3			0.040
200 – 499	104	23.0			23	35.4			81	20.9			
< 200	12	2.7			3	4.6			9	2.3			
Missing	29	6.3			3	4.6			26	6.3			
Last viral load (copies/mL)													
<50	411	90.9			59	90.8			352	91.0			0.532**
50-199	8	1.8			2	3.1			6	1.6			
>200	10	2.2			2	3.1			8	2.1			
Missing	23	5.1			2	3.1			21	5.4			
Time since diagnosis (years)	452	19.2	11.7	27.3	65	15	7.3	27	387	20.1	12.4	27.5	**0.008****
Total exposure to ART (years)	452	14.4	7.7	21.1	65	11.0	5.0	20.8	387	14.7	8.3	21.1	0.026**
CDC Category													
A	266	58.9			35	53.9			231	59.7			0.308
B	112	24.8			21	32.3			90	23.5			
C	74	16.4			9	13.9			65	16.8			
Comorbidities													
No	232	51.3			30	46.2			202	52.2			0.270
Yes	196	43.4			29	44.6			167	43.2			
Missing	24	5.3			6	9.2			18	4.7			
Depression													
No	380	84.1			54	83.1			326	84.2			0.813
Yes	72	15.9			11	16.9			61	15.8			

** results of the Chi2 analysis / † results of Student's *t*-test

Among those who met the basic requirements for the ePRO module (n=1,246), 466 had created their account at the cut-off date (4 June, 2019). Table 7 presents some of the characteristics of those who created their account compared to their counterparts. They were more often of French descent, 90.1% compared to 85.0% (p=0.036). Surprisingly, those who registered were slightly older compared to those who never registered and had been infected with HIV for longer, 19.0 ± 9.7 versus 17.8 ± 9.8 years on average (p=0.001). As follows, they were more likely to have at least one comorbidity (50.4% versus 42.6%, p<0.001).

TABLE 7 : CHARACTERISTICS OF THOSE WHO MET THE BASIC REQUIREMENTS OF THE E-PROS MODULE (N=1,246), ACCORDING TO REGISTRATION STATUS (4 JUNE 2019)

	Registered		Did not registered		Total		Chi2/ T statistic	p-value
	N	%	N	%	N	%		
Gender								
Male	370	79.4	598	76.7	968	77.7	1.77	0.413
Female	96	20.6	181	23.2	277	22.2		
Transgender	0	0.0	1	0.1	1	0.1		
Age								
<30	14	3.0	26	3.3	40	3.2	14.76	0.005
30-39	44	9.4	113	14.5	157	12.6		
40-49	89	19.1	182	23.3	271	21.8		
50-59	192	41.2	299	38.3	491	39.4		
≧ 60	127	27.3	160	20.5	287	23.0		
Transmission route								
MSM	266	57.1	410	52.6	676	54.3	2.41	0.492
Heterosexual	129	27.7	240	30.8	369	29.6		
IV Drug Use	44	9.4	80	10.3	124	10.0		
Other	27	5.8	50	6.4	77	6.2		
Country of origin								
France	420	90.1	663	85.0	1,083	86.9	8.57	0.036
Europe	11	2.4	17	2.2	28	2.3		
N/SSA Africa	28	6.0	78	10.0	106	8.5		
Americas, Asia etc.	7	1.5	22	2.8	29	2.3		
Last CD4 cell count (cells/ml)								
≧ 500	344	73.8	547	70.1	891	71.5	3.45	0.327
200 – 499	88	18.9	173	22.2	261	21.0		
< 200	6	1.3	17	2.2	23	1.9		
Missing	28	6.0	43	5.5	71	5.7		
Last viral load (copies/mL)								
<50	431	92.5	709	90.9	1,140	91.5	2.43	0.488
50-199	11	2.4	27	3.5	38	3.1		
>200	7	1.5	8	1.0	15	1.2		
Missing	17	3.7	36	4.6	53	4.3		
Hepatitis C (ever) %	81	18	152	20.49	233	19.55	1.10	0.294
Time since diagnosis (years)	466	19.0 (9.7)	780	17.8 (9.8)	1246	18.2 (9.8)	2.24	0.025
Total exposure to ART (years)	463	14.65	778	13.2	1241	13.75	3.21	0.001
Comorbidities*								
Non	201	43.1	444	56.9	645	51.8	22.26	<0.001
Yes	235	50.4	296	38.0	531	42.6		
Missing	30	6.4	40	5.1	70	5.6		

** results of the Chi2 analysis / † results of Student's *t*-test

Discussion

The QuAliV initiative's aims appear to be positively received by PLWH approached and most met the basic requirements for the IT solution. One of the important findings of this analysis is that those who were ineligible also appear to have poorer immunological and virological status compared to those who accepted. This could be due to two factors: either non-compliance linked to underlying neurological issues or language barriers (or both). It is possible that investigators prioritised patients' immediate HIV care needs rather than pushing him/her to engage with the ePROs module. Another explanation for this finding is that low socio-economic status is associated with being unable to read or understand French sufficiently well to take part in this initiative and poorer outcomes. We were not able to investigate this further due to concerns about the reliability of other indicators of socio-economic status at this stage. It will be important to investigate this in future research. Indeed, language barriers (or literacy) are an important limit of this approach and run the risk of excluding those most in need. In sister efforts in the United States, PRO are often made available in English and Spanish to accommodate migrant populations. This is more challenging in France as there is not one dominant minority language. It may be important to consider other approaches for these populations in France. For example, the use of computer-assisted self-interviewing (audio) or pictures to improve PROs collection in this population. In the United States, those who have trouble completing assessments are provided with assistance. However, it is unclear to what extent this approach can be applied to our setting. This will likely depend on the organisation within the infectious or internal disease service.

This preliminary analysis also indicates that those who were older (and met the basic requirement of the ePROs module) appeared to engage with the ePROs module (registered). One of the hypotheses is that QoL may be more of a concern for those who have been infected for a longer. Those who have been living with HIV for decades may also be more likely to engage in research. This finding is promising as we look towards the value of this approach in the context of multi-morbidity and polypharmacy. This is also reflected in observed differences in comorbidities. The greatest difference in age in terms of registration were seen in those aged 30-49, with fewer people in these two age groups not registering. It will be important to investigate whether this reflects other constraints on their time (e.g. work or family) or their health status.

Chapter 4: Measurement properties

Article 3: Assessing the psychometric properties of the French WHOQOL-HIV BREF within the ANRS CO3 Aquitaine Cohort's QuAliV Ancillary Study

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Abstract

Background: Antiretroviral therapy has prolonged people living with HIV (PLWH)'s lives, but the effects of chronic infection on health-related quality of life (HRQoL) remain a concern. Numerous instruments have been developed to measure HRQoL, yet evidence of their cross-cultural equivalence and continued applicability is limited. We analysed the psychometric properties of the French version of the WHOQOL-HIV-BREF in PLWH and examined impaired domains and facets.

Methods: We conducted a cross-sectional study nested within the ANRS CO3 Aquitaine cohort. From July 2018 to May 2019, 586 participants were consecutively enrolled at their HIV-consultations and completed either a web-based (n=406) or paper self-administered questionnaire (n=180). The mean, SD, floor and ceiling effects were computed. Internal consistency and construct validity were assessed using i) Cronbach's alpha coefficients per domain and ii) Confirmatory Factor Analysis (CFA). Concurrent, convergent and discriminant validity were assessed with Pearson's correlations and known-groups validity, according to CD4 T cell count, viral load and CDC disease stage categories, were assessed. Differences in mean domain scores according to sex, country of origin, and transmission groups were then evaluated.

Results: 586 PLWH were included in this analysis. Their median age was 56, 73% were male; 85% were of French descent; 99% were on ART and 93% were virally suppressed. We found floor effects for one and ceiling effects for 11 items. The six-domain structure showed acceptable internal consistency (α range: 0.63-0.79). CFA showed that the WHOQOL-HIV BREF's six-domain structure produced an acceptable fit (SRMR = 0.059; CFI= 0.834; RMSEA= 0.07; 90% CI: 0.06 - 0.08). It showed good concurrent, convergent and some evidence of discriminant validity. The personal beliefs domain had the highest score (15.04 ± 3.35) and the psychological health domain had the lowest (13.70 ± 2.78). The most impaired facets were personal relationships (2.7 ± 1.25) and financial resources (2.9 ± 1.15). Women reported significantly lower scores compared to men for 12/29 facets, including all five HIV-specific facets.

Conclusions: The French WHOQOL-HIV BREF has acceptable measurement properties. Its broad conceptualisation of HRQoL, going beyond physical and mental health, may be of particular value in our older, treatment-experienced and virally suppressed population.

Trial registration: ClinicalTrials.gov NCT03296202

Keywords: HIV, health-related quality of life, WHOQOL-HIV BREF,

Introduction

The benefits of early and sustained access to potent antiretroviral therapy (ART) for people living with HIV (PLWH) are now clear. Early ART conveys a double benefit. It improves the health of individuals (decreased risk of AIDS-related and non-AIDS related diseases) and, by lowering their viral load to undetectable levels, reduces the risk they will transmit the virus to others [27, 96]. Sustained viral suppression has increased PLWH's longevity [6]. Unfortunately, it has not enabled their full return to health [38]. In countries and regions where most PLWH are diagnosed, linked to care and have sustained access to effective ART, there have been resounding calls to "go beyond viral suppression" and, more specifically, to formally consider "good health-related quality of life (HRQoL)" as the ultimate metric of health system performance [71]. There is therefore a need for valid and reliable instruments to assess HRQoL.

A number of instruments have been developed to measure HRQoL in PLWH. A recent systematic review of reviews on measuring quality of life in PLWH by Cooper et al. catalogue instruments, both generic and disease-specific, used to measure HRQoL in PLWH. They identified nine generic instruments and seven disease-specific instruments that were comprehensive (covering at least three domains), could be self-administered in 10 minutes, and had been developed with input from PLWH [52]. The WHOQOL-HIV BREF covers six generic domains: physical, psychological, level of independence, social, environmental and spiritual quality of life [13]. It together with the PROQOL-HIV [97] were considered to have "promising psychometric properties and be more relevant to PLWH compared to MOS-HIV" [57], which has the most well-established psychometric properties but limited cross-cultural relevance and continued applicability [52]. The authors highlight the need for further validation of HRQoL measures in new populations and longitudinally.

Aims

We aim to assess the psychometric properties of the WHOQOL-HIV BREF instrument [13], administered in both electronic and paper form to a population of PLWH in Nouvelle Aquitaine, France to ensure cross-cultural relevance and continued applicability in our older, more treatment-experienced and mostly virally suppressed population. More specifically, we evaluate the distribution of item and domain scores, internal consistency, construct validity, convergent and discriminant validity, known-group validity. We also examine differences in mean item and domain scores according to sex, country of origin, and transmission route.

Methods

The ANRS CO3 Aquitaine cohort is a prospective longitudinal study of adults (≥ 18 years old) with a confirmed HIV-1 diagnosis and in care in 13 public hospitals in the Nouvelle Aquitaine region of south-western France. Qualified clinical research technicians routinely collect epidemiological, clinical and biological data from patients' medical records and enter them in a web-based electronic Case Report Form called ARPEGE 1.0.

The QuAliV study is a cross-sectional study nested within the ANRS CO3 Aquitaine cohort, ongoing since mid-July 2018. Patients meeting the cohort's eligibility criteria were enrolled during their routine hospital-based HIV-consultation. Investigators invited eligible patients to participate in this ancillary study online or, if the patient did not have a personal email account or reliable Internet access, via a self-administered paper questionnaire following their consultation. Theoretically eligible patients were deemed ineligible if they did not understand and/or read French or if they were severely neurologically or psychologically impaired. As described in detail elsewhere [11], those who accepted the invitation were issued a personal study-specific unique identifier, which enabled them to independently create an account. An identical paper questionnaire was issued to those who did not have a personal e-mail account or reliable internet access. They were allowed to complete the questionnaire immediately or mail it back to the hospital.

A series of validated paper questionnaires was chosen by a steering committee based on their established measurement properties and pragmatic considerations (i.e. self-administration, availability in French, length etc.). We used translations of items from the validated French WHOQOL-BREF [98] and the validated French 100-item WHOQOL-HIV [99] to form the French WHOQOL-HIV BREF in consultation with staff at the World Health Organisation. Cognitive debriefing was performed with native-speakers to ensure that items had good face validity (Annex V). Paper-versions of questionnaires were adapted to a screen format following the International Society for Quality of Life Research's recommendations [17]. Before launching the pilot study, empirical, task-based usability evaluations were conducted on two successively developed prototypes of the electronic PROs module of the ANRS CO3 Aquitaine cohort's data capture and visualization system [95].

This analysis covers the period of the initial 10-months of implementation (July 23, 2018 – June 4, 2019) in five clinics: Bordeaux (n=3), Bayonne (n=1), and Périgueux (n=1). Participants consulting between July 23, 2018 – May 15, 2019 and invited to participate were considered for this analysis if they had provided informed consent and had at least one recorded hospital consultation or hospitalisation between the 1st of January 2017 and the 6th of June 2019. They were considered to have "registered" if their account was created on or by June 4th 2019 or if a paper questionnaire had been completed and returned

to the clinics before this date. All available self-reported data, saved as participants progressed through each stage of the questionnaire, were considered for analysis if they pertained to participants who were seen at hospital during the fixed study period, independently of whether or not they had locked/submitted their questionnaires. Paper questionnaires, which had been returned prior to the 4th of June, were entered. As we intended to perform a confirmatory factor analysis (CFA), we followed Kline's guidance suggesting 10 to 20 observations per estimated parameter, where the number of identifiable parameters is, for the simplest of models encompassing k items, Np = k x (k+1)/2 (17). Assuming that k equals 29 for the WHOQOL-HIV BREF, we calculated an Np equal to 435.

Data sources and variables

The WHOQOL-HIV BREF is a 31-item self-reported questionnaire covering six domains with 29 items: physical (4 items), psychological (4 items), level of independence (4 items), social relationships (4 items), environmental (8 items) and spiritual (4 items) and two general items that measure overall quality of life and general health. Each item is rated on a 5-point Likert scale, where 1 denotes poor and 5 excellent. To obtain individual domain scores, negatively phrased items are reverse scored. The domain scores are then calculated by multiplying the mean of all items within the domain by 4. This results in six domain scores, each ranging from 4 (worst) to 20 (best). Participants also self-reported their educational attainment (ranging from none to 5 years post-secondary education or higher), net household income (ranging from less than 900€ to more than 4000€ per month), profession, employment status, and whether or not they lived with a partner.

Patients' self-reported data were merged with those routinely collected from patients' medical records at either enrolment or at the most recent recorded hospital consultation and extracted on the 6th of June 2019. We derived the participant's age, transmission route, coded as men having sex with men (MSM), intravenous (IV) drug use, or other, country of origin, time in years since HIV diagnosis, time in years since start of first antiretroviral treatment, and HIV stage according to CDC categories. Participants' most recent CD4 T counts (cells/mm^3) and viral load (copies/mL) were considered if they were collected within three-year window of the most recent consultation. CD4 T cell counts were categorised according to the following thresholds <200, 200-499, and ≥500 cells/mm^3. Viral load measures are presented according to the following thresholds <50, 50-200, >200 copies/mL and as the proportion of patients with a viral load <50 copies/mL.

Statistical analysis

All analyses were performed using STATA 15.1 (StatCorp LLC). Participants' sociodemographic and HIV-related characteristics are described. Frequencies and proportions are presented for categorical

variables, and median as well as the 25th and 75th quartiles are presented for continuous variables. The six domain scores were calculated for those with complete data. We computed the proportion of missing responses for each item, omitting the first two items on general quality of life and health status that were compulsory in the questionnaire. We also computed the mean, standard deviation (s.d.), skewness, kurtosis, floor and ceiling effects of each item and domain. We assumed that there was a floor or ceiling effect if more than 20% of responses were in extreme categories (either 1 or 5). We evaluated internal consistency for each domain using the Cronbach's alpha. To test construct validity, we performed a CFA based on the original six-domain structure and assessed the pattern of item-factor relationships (factor loadings). It has been recommended that items with low factor loadings (e.g. below 0.2 or 0.3) be removed from the instrument [100]. We assessed goodness of fit using the approximate goodness-of-fit indices rather than the chi-square goodness-of-fit test based on Fayer and Machin's recommendations [45]. As per Hu and Bentler's guidance, we presented the Standardised Root Mean Square Residual (SRMR) as well as the Comparative Fix Index (CFI) and the Root Mean Square Error of Approximation (RMSEA) [101]. The proposed threshold for the SRMR is <0.08. For the CFI, values >0.95 are commonly used to indicate good fit and values of >0.90 indicate acceptable fit; for the RMSEA, 0.05 is considered excellent fit whereas 0.08 acceptable fit. The WHOQOL-HIV BREF's concurrent validity was examined using Pearson's correlations between domains and general perceptions of quality of life (item 1) and general health (item 2). We tested convergent and discriminant validity by calculating item-domain Pearson's correlations. A correlation coefficient >0.4 for items and their respective domains was considered to be satisfactory. Items revealing correlations with their respective domains that were higher than those with other domains will be used to indicate good discriminant validity [45].

Known-groups validity or the ability of the instrument to discriminate between specified groups of patients was assessed according to participants' immunological (CD4 T cell count) and virological status (viral load copies/mL). We expected that participants with higher CD4 T cell counts would have higher HRQoL. Conversely, we expected those with a detectable viral load, defined as >50 copies/mL, to have poorer HRQoL. We also repeated analyses conducted by O'Connell and Skevington exploring mean differences in domain scores in three subgroups: HIV-asymptomatic, HIV-symptomatic, and AIDS, using ANOVA [13].

We performed additional analyses according to sex (male versus female) using Student's t-tests and calculated Cohen's d as a measure of effect size per item and domain. We compared mean domain scores according to country of origin i) France versus Foreign using Student's t-test and ii) France (reference category) versus Europe, North/Sub-Saharan Africa, or Asia/Americas using simple linear regression. We then assessed whether there was evidence of a difference in mean dimension scores in heterosexuals,

IV drug users and other routes of transmission compared to MSM (reference category) using simple linear regression.

Results

Basic characteristics

The WHOQOL-HIV BREF questionnaire was completed by 587 PLWH during the study period. One observation was excluded due to delays in clinical data entry at clinical sites. 586 participants having completed at least the first item of the WHOQOL-HIV BREF were therefore considered for this analysis, 406 (69.3%) completed an electronic version of the questionnaire and 180 (30.7%) an identical paper version. Five-hundred and four participants had complete all items for the physical health, 569 for psychological health, 560 for level of independence, 557 for social relations, 557 for environmental health and 570 for personal beliefs domains. The study population's characteristics are described in detail in Table 8. Respondents were mostly male (n=430, 73.2%) and their median age 55.8 years old (48.9, 62.8). Eighty-five percent were of French descent. Forty-two percent (n=248) reported living with a partner. The main transmission group was MSM (n=290, 49.5%) followed by heterosexual contact (n=192, 32.8%). The median time since HIV diagnosis was 19.6 ± 9.7 years. Participants were treatment-experienced, with a median time since first ART of 16.4 years (8.3, 21.7). The vast majority (92.7%) were virally suppressed.

TABLE 8 : SOCIO-DEMOGRAPHIC AND HIV CHARACTERISTICS OF THE STUDY POPULATION (N=586)

	N	%/Median (25th,7th percentile)		N	%/Median, (25th,75th percentile)
Median age (years, IQR)	586	55.8 (48.9 - 62.8)	Transmission Category (%)		
Sex (N, % male)	586	430 (73,2)	MSM	290	49.5
Level of education (%)			Heterosexual	192	32.8
None	40	6.8	IV Drug Use	66	11.3
Primary education	43	7.4	Other	38	6.5
Secondary education	19	3.3			
Vocational training	140	23.9	CDC category C (%)	117	20.1
High school edu	132	22.5			
Associates	72	12.2	Last CD4 cell count (cells/ml, %)		
Undergraduate	62	10.5	≧ 500	422	72.0
Master's	69	11.8	200 – 499	114	19.5
Do not know	9	1.5	< 200	15	2.6
			Missing	35	6.0
Profession (%)					
Labourer	60	10.2	Last viral load (copies/mL, %)		
Farmer	3	0.5	< 50	543	92.7
Intermediate occupation	56	9.6	50-200	14	2.39
Employee	138	23.5	≧ 200	11	1.9
Artisan, Business owner	43	7.3	Missing	18	3.1
Middle manager, executive	235	40.1			
Do not wish to reply	51	8.8	Median time since start of ART (years, IQR)		
				583	16.4 (8.3 - 21.7)
Household income (%)					
Less than 900 €	84	14.3			
900 - 1499 €	131	22.4			
1500 - 2000 €	103	17.6			
2001 - 3000 €	96	16.4			
3001 - 4000 €	65	11.1			
More than 4000 €	60	10.2			
Do not wish to respond	47	8.0			
Place of origin (%)					
France	498	85.0			
Europe	15	2.6			
N/SS Africa	63	10.8			
Asia, Americas, Oceania	10	1.7			

* Completed at least 1st item of the WHOQOL-HIV BREF questionnaire : How would you rate your quality of life?

Score distributions

The descriptive statistics of each item and domain are presented in Table 9. The proportion of missing item-level responses ranged from 0.7-2.6%. The items with most missing responses were “How much do you need any medical treatment to function in your daily life?” and “How satisfied are you with your personal relationships?” All items were negatively skewed. Five of the 31 items pertaining to activities of daily living, physical environment, health and social care, transportation and forgiveness and blame were strongly skewed to the left with coefficients of less than – 1.0. Kurtosis coefficients, measuring the heaviness of the tails of the distribution, ranged between 1.87 and 4.7. Floor effects were found for one item pertaining to “personal relationships”, with 22.4% of respondents responding in the lowest category. Ceiling effects were detected in 11 out of 31 items. Overall, the spirituality and personal beliefs domain had the highest score (15.04 ± 3.35) and the psychological health domain had the lowest score (13.70 ± 2.78).

TABLE 9: DESCRIPTIVE STATISTICS OF THE FRENCH WHOQOL-HIV BREF (N=586)

Domain or item	N	Missing (%)	Mean	SD	Skewness	Kurtosis	Floor effect (%)	Ceiling effect (%)
Overall QOL/General Health								
Overall Quality of life	586	-	3.67	0.80	-0.45	3.43	1.0	12.6
General health perception	586	-	3.55	0.95	-0.74	3.15	3.1	10.8
I. Physical health	**574**		**14.15**	**2.96**				
Pain and discomfort *	582	0.7	3.93	1.10	-0.72	2.56	2.4	41.1
HIV symptoms *	580	1.0	3.80	1.14	-0.56	2.31	3.0	36.1
Energy and fatigue	582	0.7	3.35	0.89	-0.36	3.00	2.8	7.1
Sleep and rest	578	1.4	3.06	1.17	-0.35	2.11	13.6	7.3
II. Psychological health	**569**		**13.70**	**2.78**				
Positive feelings	581	0.9	3.33	0.96	-0.51	3.19	5.7	8.7
Concentration	577	1.5	3.80	0.92	-0.38	2.87	1.7	14.9
Bodily image and appearance	582	0.7	3.13	1.07	-0.33	2.69	10.2	9.0
Self-esteem	577	1.5	3.52	0.93	-0.67	3.39	3.6	10.8
Negative feelings *	578	1.4	3.54	1.00	-0.62	3.10	4.3	14.4
III. Level of independence	**560**		**14.65**	**3.49**				
Dependence on medication or treatment	571	2.6	3.32	1.55	-0.22	1.49	17.4	37.5
Activities of daily living	583	0.5	4.14	0.97	-1.13	3.83	1.9	44.3
Work capacity	579	1.2	3.69	0.94	-0.82	3.48	2.8	16.3
Mobility	573	2.2	3.49	1.14	-0.76	2.82	9.1	15.6
IV. Social relations	**557**		**13.91**	**3.03**				
Social support	577	1.5	3.85	0.96	-0.96	3.90	3.1	24.1
Sexual activity	577	1.5	3.67	0.91	-0.96	4.06	3.5	12.9
Personal relationships	571	2.6	2.77	1.25	-0.02	1.87	22.4	7.2
Social inclusion	574	2.0	3.64	0.99	-0.79	3.60	4.9	17.0
V. Environmental health	**557**		**14.37**	**2.57**				
Physical safety and security	582	0.7	3.51	0.99	-0.79	3.52	6.4	12.0
Home environment	582	0.7	3.53	1.14	-0.84	3.06	9.6	16.8
Financial resources	577	1.5	2.90	1.15	-0.16	2.35	16.8	7.8
Opportunities to acquire new skills and information	580	1.0	3.65	0.94	-0.79	3.53	3.1	14.5
Participation in and opportunities for recreation and leisure activities	578	1.4	3.02	1.15	-0.27	2.27	13.8	7.8
Physical environment	577	1.5	3.98	0.96	-1.20	4.56	3.3	30.3
Health and social care	576	1.7	4.16	0.83	-1.18	4.72	0.9	36.6
Transport	576	1.7	3.95	0.96	-1.11	4.33	3.3	29.0
VI. Spirituality/religion and personal beliefs	**570**		**15.04**	**3.35**				
Religion, spirituality and personal beliefs	580	1.0	3.35	1.18	-0.51	2.44	10.0	15.2
Forgiveness and blame *	580	1.0	4.28	1.19	-1.47	3.88	4.3	67.1
Concerns about the future *	580	1.0	3.62	1.23	-0.58	2.36	7.1	29.1
Death and dying *	578	1.4	3.80	1.24	-0.74	2.50	6.4	39.3

* items which were reverse coded

Reliability

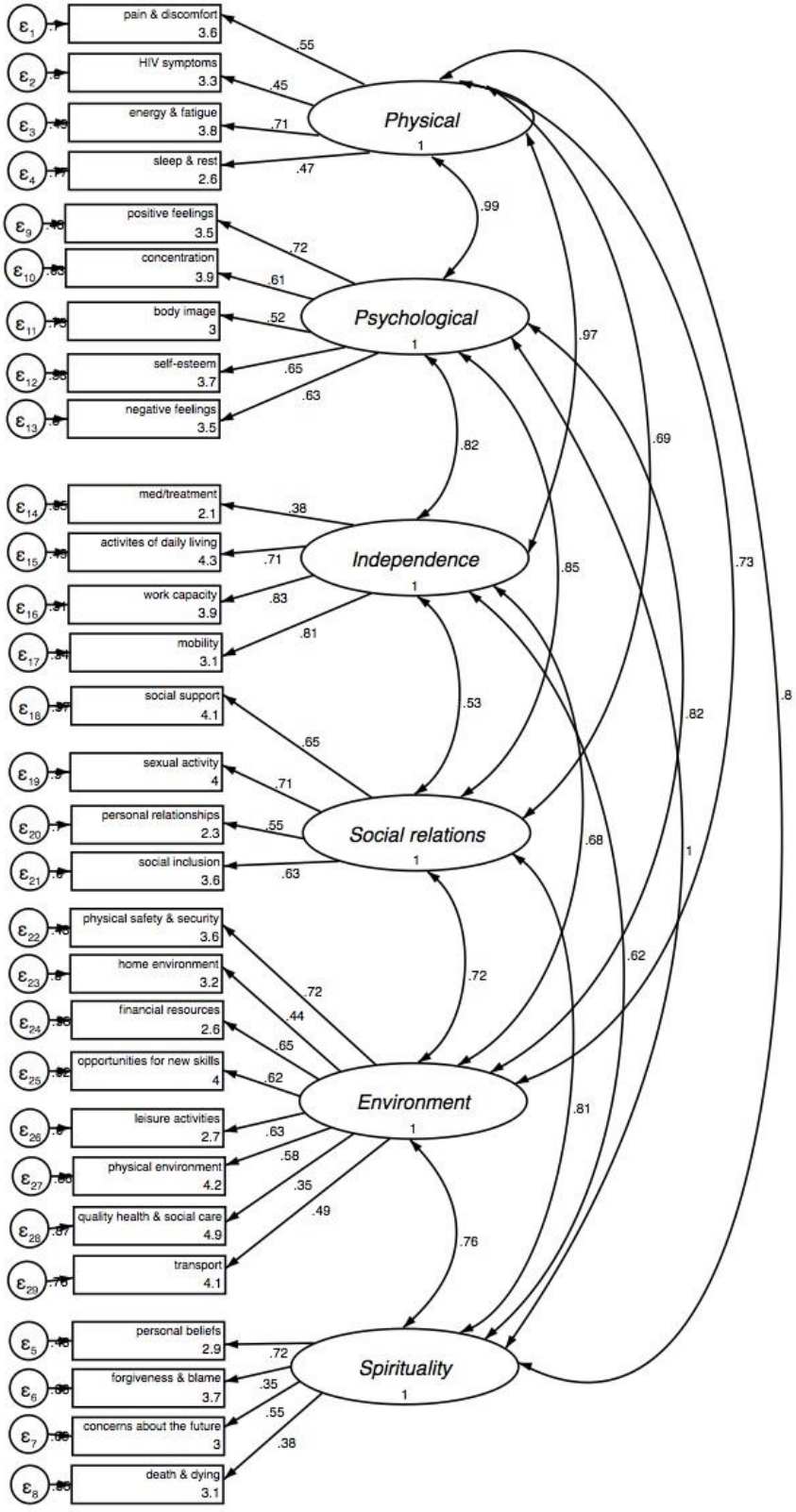
The six-domain structure showed an acceptable internal consistency (Cronbach's α ranged from 0.63 to 0.79) (Table 10). The physical health and the spirituality domains had a Cronbach α of 0.63 and 0.64 respectively, which are somewhat below the threshold of 0.70 for acceptable internal consistency.

TABLE 10 : INTERNAL CONSISTENCY OF THE WHOQOL-HIV BREF

Domain	N	Mean	SD	Range Min	Range Max	Cronbach's α Coeff.
I. Physical health	574	14.15	2.97	4	20	0.63
II. Psychological health	569	13.70	2.78	4.8	20	0.76
III. Level of independence	560	14.65	3.49	4	20	0.72
IV. Social relations	557	13.91	3.03	4	20	0.70
V. Environmental health	557	14.37	2.57	6	20	0.79
VI. Spirituality/religion and personal beliefs	570	15.04	3.35	4	20	0.64

Construct validity

The CFA results (Figure 8) showed that the six-domain structure of the WHOQOL-HIV BREF produced an acceptable fit to the data (SRMR = 0.059; CFI=0.834; RMSEA = 0.070; 90% CI: 0.066–0.075). The factor loading of each item with its respective domain was acceptable, ranging from 0.35 to 0.83.



The structure of the French version of the WHOQOL-HIV BREF based on Confirmatory Factor Analysis. Factor loadings between manifest variables (items) and latent traits (domains) are standardized coefficients. Standardized covariances are also shown between all latent traits (domains). Standardised Root Mean Square Residual (SRMR) = 0.059; Comparative Fit Index (CFI) was equal to 0.834 and Root mean square error of approximation (RMSEA) and equal to 0.07 (90% CI 0.06 - 0.08).

FIGURE 8 : SIX-FACTOR STRUCTURE OF THE WHOQOL-HIV BREF

Concurrent validity

The correlation coefficients of all domains with the two general measures (general QOL and general health status) with each of the six domains is presented in Table 11. All domains correlated with both general quality of life (How would you rate your quality of life?) and general health status (How satisfied are you with your health?) significantly ($p<0.001$). With the exception of the domain pertaining to spirituality and personal beliefs, the correlation coefficients were greater than 0.40 (range of r=0.44-0.59) for domains and general perception of quality of life. Correlations between domains and general health status were weaker, with correlation coefficients ranging from 0.33-0.47. Physical and psychological health correlated more strongly with general health status than other domains (Table 11).

TABLE 11 : CONCURRENT VALIDITY OF THE WHOQOL-HIV BREF

		Correlation coefficient			
Domain	N	General QoL		General health status	
I. Physical health	574	0.54	***	0.47	***
II. Psychological health	569	0.59	***	0.47	***
III. Level of independence	560	0.51	***	0.44	***
IV. Social relations	557	0.44	***	0.33	***
V. Environmental health	557	0.57	***	0.39	***
VI. Spirituality/religion and personal beliefs	570	0.38	***	0.33	***
*** : p<0.001, results of Pearson's					

Convergent and discriminant validity

Items were generally strongly correlated with their respective domains, with correlation coefficients ranging from 0.45 to 0.82. All but one item were more highly correlated with their respective domains than other domains; the item regarding the spiritual domain (Question n°7: To what extent do you feel your life to be meaningful?) showed a higher correlation with the psychological domain (r = 0.67) than with the personal beliefs and spirituality domain (r = 0.47). Otherwise, convergent and discriminant validity were considered to be good (Table 12).

TABLE 12 : CONVERGENT & DISCRIMINANT VALIDITY OF THE WHOQOL-HIV BREF

Domain	Range correlation coefficient				Convergent Validity		Discriminant validity	
	convergent validity		discriminant validity		Success ✦ / Total	%	Success ✧ / Total	%
	min	max	min	max				
I. Physical health	0.65	0.72	0.27	0.65	4/4	100	4/4	100
II. Psychological health	0.67	0.77	0.31	0.56	5/5	100	5/5	100
III. Level of independence	0.70	0.80	0.21	0.63	4/4	100	4/4	100
IV. Social relations	0.73	0.75	0.28	0.57	4/4	100	4/4	100
V. Environmental health	0.45	0.71	0.12	0.61	8/8	100	8/8	100
VI. Spirituality/religion and personal beliefs	0.58	0.82	0.15	0.66	4/4	100	3/4	75

✦ Success : a correlation coefficient ≧ 0.4 for items and their respective domain

✧ Success : a correlation coefficient for item greater in respective domain compared to other 5 domains

Known groups validity

The WHOQOL-HIV-BREF was not able to discriminate based on immunological and virological status (results not shown). We explored known-groups validity according to CDC defined HIV clinical categories for HIV infection [102]. Both overall quality of life and general health status and domain scores were higher for those classified in clinical category A, which reflects asymptomatic HIV infection in other words those without a history of symptoms or AIDS-defining conditions, compared clinical category B, which reflects HIV infection with symptoms directly attributable to HIV infection. However, no differences were detected between categories B and C (AIDS) (Table 13).

TABLE 13: KNOWN-GROUPS VALIDITY OF THE WHOQOL-HIV BREF INSTRUMENT ACCORDING TO CDC CLINICAL CATEGORIES FOR HIV INFECTION

		A				B				C			F	
		N= 330				N = 136				N = 117				
Overall QoL and Health	N	Mean	95% CI		N	Mean	95% CI		N	Mean	95% CI			
General QoL ‡ (N=586)	333	3.78	3.70	3.86	136	3.57	3.44	3.71	117	3.50	3.35	3.64	7.09	**
General Health Status ‡ (N = 586)	333	3.67	3.57	3.76	136	3.36	3.19	3.53	117	3.43	3.25	3.60	6.46	**
Domain														
I. Physical health ‡ (N = 574)	326	14.55	14.25	14.86	135	13.61	13.09	14.14	113	13.63	13.06	14.20	7.11	**
II. Psychological health ‡ (N = 569)	324	13.98	13.67	14.28	132	13.21	12.73	13.68	113	13.51	12.99	14.02	3.98	*
III. Level of independence ‡ (N = 560)	317	15.18	14.82	15.55	131	13.92	13.26	14.57	112	14.00	13.38	14.62	8.73	**
IV. Social relations ‡ (N = 557)	316	14.12	13.78	14.45	131	13.43	12.89	13.96	110	13.88	13.35	14.41	2.42	
V. Environmental health ‡ (N = 557)	318	14.68	14.42	14.94	130	14.05	13.57	14.52	109	13.86	13.33	14.39	5.62	**
VI. Spirituality/religion and personal beliefs ‡ (N=570)	325	15.30	14.95	15.66	132	14.53	13.95	15.11	113	14.90	14.26	15.55	2.63	

* ANOVA ; * $p < 0.01$ ** $p < 0.001$

‡ Category A is significantly different than category B based on T-test; No differences detected between B and C categories.

Women reported significantly lower scores compared to men for 12/29 facets, including all five HIV-specific facets. Women also reported lower domain scores compared to men in the environmental and personal beliefs domain (Table 14). Those born in North or Sub-Saharan Africa had poorer environmental health domain scores compared to those born in France (13.19 ± 2.10 versus 14.52 ± 2.56, $p < 0.001$). Otherwise, no differences were detected between those born elsewhere versus those born in France. Those who contracted HIV via IV drug use reported lower physical health, psychological health, level of independence and environmental health compared to MSM. However, there were no differences detected in mean scores between other transmission groups and MSM.

TABLE 14: KNOWN-GROUPS VALIDITY OF THE WHOQOL-HIV BREF INSTRUMENT ACCORDING SEX

Domain or item	Sex					
	Male (n = 430)		Female (n=156)			
	Mean	**SD**	**Mean**	**SD**	**p-value ◊**	**Cohen's d †**
Overall QOL/General Health						
Overall quality of life	3.7	0.8	3.6	0.8	0.182	0.12
General health perception	3.5	0.9	3.6	1.0	0.299	-0.10
I. Physical health	14.3	2.9	13.8	3.1	0.061	0.18
Pain and discomfort *	4.0	1.1	3.8	1.1	0.201	0.12
HIV symptoms *	3.9	1.1	3.6	1.3	0.038	0.20
Energy and fatigue	3.4	0.9	3.3	0.9	0.554	0.06
Sleep and rest	3.1	1.2	3.0	1.2	0.317	0.09
II. Psychological health	13.8	2.8	13.4	2.8	0.098	0.16
Positive feelings	3.4	0.9	3.2	1.0	0.011	0.24
Concentration	3.6	0.9	3.5	1.0	0.063	0.18
Bodily image and appearance	3.2	1.0	3.0	1.2	0.096	0.16
Self-esteem	3.5	0.9	3.7	0.9	0.045	-0.19
Negative feelings *	3.6	1.0	3.4	1.0	0.043	0.19
III. Level of independence	14.8	3.4	14.3	3.7	0.147	0.14
Dependence on medication or treatment *	3.4	0.9	3.2	1.0	0.011	0.24
Activities of daily living	3.3	1.6	3.3	1.6	0.783	-0.03
Work capacity	4.2	1.0	4.0	4.0	0.108	0.15
Mobility	3.5	1.1	3.3	1.3	0.029	0.21
IV. Social relations	13.9	3.0	13.9	3.3	0.837	0.02
Social support	3.9	0.9	3.7	1.2	0.034	0.20
Sexual activity	3.6	0.9	3.8	0.9	0.161	-0.13
Personal relationships	2.8	1.2	2.8	1.4	0.878	-0.01
Social inclusion	3.6	1.0	3.6	1.0	0.960	0.00
V. Environmental health	14.5	2.5	13.9	2.6	0.006	0.27
Physical safety and security	3.6	0.9	3.4	1.1	0.033	0.20
Home environment	3.5	1.1	3.5	1.2	0.592	0.05
Financial resources	3.0	1.1	2.5	1.2	<0.0001	0.44
Opportunities to acquire new skills and information	3.7	0.9	3.6	1.0	0.265	0.11
Participation in and opportunities for recreation and leisure activities	3.2	1.1	2.6	1.3	< 0.0001	0.51
Physical environment	4.0	1.0	4.0	1.0	0.915	-0.01
Health and social care: accessibility and quality	4.1	0.9	4.3	0.8	0.077	-0.17
Transport	4.0	0.9	3.9	1.0	0.051	0.05
VI. Spirituality/religion and personal beliefs	15.3	3.2	14.4	3.7	0.011	0.25
Religion, spirituality and personal beliefs	3.3	1.2	3.4	1.2	0.891	-0.01
Forgiveness and blame *	4.4	1.1	4.0	1.4	0.001	0.32
Concerns about the future *	3.7	1.2	3.4	1.4	0.023	0.21
Death and dying *	3.9	1.2	3.6	1.3	0.050	0.18

* Reversed items recoded

◊ Results of a Student's t-test

† Cohen's d is a measure of effect size between two means, 0.20: small effect size, 0.50 medium effect size, 0.80 a large effect size

Discussion

The WHOQOL-HIV BREF was selected for use in our patient population for many of the reasons put forth by Cooper et al. [52]. First, it was created more recently than other disease-specific instruments, many of which were either developed prior to or shortly after effective ART [57]. Second, it was developed simultaneously in six culturally-diverse countries, making its cross-cultural equivalence potentially superiour to instruments developed in a single population [13]. Third, the majority of items were generic as they stemmed from the WHOQOL-BREF instrument [103]. Finally, HIV is mentioned only twice in the phrasing of questions. This was relevant given the conclusions of previous studies of HRQoL in PLWH compared to the general population [104] that poorer HRQoL may in part be due to factors other than HIV infection.

The French version of the WHOQOL-HIV BREF presented acceptable measurement properties in our population of older, treatment-experienced and virally suppressed patients. We did, however, observe ceiling effects for a number of items. Some of these are expected, given our sample's clinical characteristics and the current standard of HIV care in [south-western] France. For example, ceiling effects were observed for physical pain and HIV symptoms, with 41.1% responding that they were not at all hampered by physical pain and 36.1% stating that they were not at all bothered by physical problems related to HIV. We observed the greatest ceiling effect for the item pertaining to forgiveness and blame (To what extent are you bothered by people blaming you for your HIV status?), with 67.1% responding that they were not at all bothered.

CFA suggested acceptable fit to our data. The SRMR suggested good model fit. CFI, which compares the fit of a target model to the fit of an independent or null model, and RMSEA, measuring the discrepancy between the observed and model-implied covariance matrices, adjusted for degrees of freedom, suggested acceptable model fit. Furthermore, all the first-order factor loadings were either high to moderately high. We, therefore, do not recommend that these items be removed from the WHOQOL-HIV BREF questionnaire. Nevertheless, one item from the spiritual health domain appeared to be better correlated with the psychological health domain.

Somewhat unsurprisingly given the clinical characteristics of those currently in care, the WHOQOL-HIV BREF questionnaire was not able to discriminate between different CD4 T cell count subgroups (most recent measurement within three years of the last consultation). One reason for this finding may be the fact that 99% of the participants were on ART and only 2.6% of the participants in the current study were significantly immunosuppressed, with CD4 T cell counts below 200 cells/mm^3 within the

past three years. Nevertheless, there was some evidence of a difference in both general items and domain scores between CDC clinical category A compared to those in clinical category B. However, we were not able to detect a difference between categories B and C. Immune restoration as a result of ART provides some explanation for the absence of differences between categories B and C [105].

Previous studies have been conducted to assess the validity of Portuguese [106], Spanish [107], Finnish [108], Chinese [109], Malay [110], Taiwanese [111], Persian [112] versions of the WHOQOL-HIV BREF. Our findings regarding the WHOQOL-HIV BREF's less than ideal internal consistancy are similar to those of Nobre [108], Hsiung [111], Zhu [109], and Fuster-Ruizde Apodaca [107] who also reported lower internal consistency in the physical health and spirituality/personal beliefs domains compared to the other four domains. As to the instrument's ability to discriminate between known-groups, specifically those based on CD4 T cell count thresholds, findings have been mixed. Some have reported that WHOQOL-HIV BREF detected differences between CD4 T cell count groups [107, 109]; while others like Nobre et al., in a population quite similar to ours in Finland, have not been able to detect a difference [108].

Strengths & Limitations

Given the effort, money and time required to develop a new instrument designed to measure a multi-dimensional construct like [HR]QoL, many have urged researchers to rely on existing instruments and ensure their validity in new populations. We have followed this recommendation. However, we enrolled PLWH on a voluntary basis in clinic and relied on their willingness and ability complete a self-administered assessment. This resulted in the exclusion of people who had severe neurocognitive impairment or were not able to understand and/or read French sufficiently well. This recruitment strategy may have resulted in a less representative sample of French-speaking people in care in 2019. We could not assess test-retest reliability as only one time point was available at the time of this analysis. We could not assess concurrent validity compared to other questionnaires, only general items. We did not explore measurement invariance between different subgroups, for example, between men and women, as only 156 women had responded. These are areas for future research.

Conclusions

The WHOQOL-HIV BREF, going beyond physical and mental health, has acceptable measurement properties in our older, treatment-experienced and virally suppressed population. Our findings also shed

light on some of its potential shortcomings, which are relevant for future research in an era where an increasing number of PLWH are doing well on ART.

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Competing interests

DB has received speaking fees from Gilead. FB declares to have received reimbursement for attending a symposium from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen; speaking fee and consultancy fee from ViiV Healthcare, Gilead, Bristol-Myers Squib, Merck and Janssen; and funds for research from Gilead and ViiV Healthcare. The other authors declare that they have no competing interests.

Authors' contributions

DB, FD and FB designed the QuAliV study and secured its funding. DB analysed data and drafted the manuscript. MH, DN, M-OV, EL, PD, NR, and FB recruited study participants as investigators at participating sites and reviewed the manuscript. OL contributed to the study’s design and implementation and critically reviewed the manuscript. FM, LW, FB contributed to analysis and critically reviewed the manuscript. ME acted as a patient representative in the study’s steering committee and thus contributed to the study’s design. All authors read and approved the final manuscript.

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4. Discussion of lessons learned and ongoing and future research

This thesis presents the conception, including formative research, and initial implementation of a novel (research) initiative undertaken to better capture PROs, including QoL, in PLWH in long-term hospital-based care in the Nouvelle Aquitaine region of southwestern France.

Regulatory consideration

We had first approached this project as a one-off study examining QoL in PLWH in the current treatment era and in a context in which the UNAIDS' 90-90-90 targets had already been achieved. However, we quickly realised that by nesting this study within the ANRS CO3 Aquitaine cohort, we had the potential to better capture (and ultimately address) not only HRQoL but also other patient-report outcomes and do so longitudinally. We drew inspiration from both sister initiatives in the United States and other disease areas where PROs are commonly used for both research and care. But, by choosing to develop an ePRO module linked to the ANRS CO3 Aquitaine cohort's data capture and visualisation system, we were in fact amending the cohort's protocol, by deviating from the data collection and storage methods, which had already been granted ethical approval. Furthermore, as the implementation of the ePROs module requires patients to use their email addresses to create their personal accounts, an amendment to the regulatory authorisations, previously granted by The French National Commission on Informatics and Liberty, an independent administrative regulatory body charged with ensuring that data privacy laws are applied to the collection, storage, and use of personal data, was requested in late 2017 and approval was granted on March 12, 2018.

The "QuAliV" study, designed as an ancillary study of the current iteration of the ANRS Aquitaine cohort, sponsored by the University Hospital of Bordeaux, is, in its first iteration, a cross-sectional study nested in the "AQUIVIH" cohort. Designing this study within the ANRS CO3 Aquitaine cohort had a number of advantages. It has allowed for linkage to structured epidemiological, clinical and biological data abstracted from participants' medical records, a strength not shared by many studies on HRQoL in PLWH. We were also able to draw on the cohort's human resources, namely its project team and CRAs. However, by conducting this research within the cohort, we were somewhat limited from a regulatory perspective in terms of the scope of the ePRO module. The "loi Jardé" or the law governing biomedical research in France divides research on human subjects into three categories. Category 1 refers interventional research (not justified within usual care), category 2 refers to interventional research with minimal risks and constraints and category 3 refers to non-interventional research. The ANRS CO3 cohort would otherwise fall into category 3; however, the addition of a self-administered questionnaire

changes its designation to category 2 in the eyes of the loi Jardé. Had additional features inciting changes to patient care been added to the ePRO module, it might have complicated matters from a regulatory perspective. It was decided to begin with the proposed data collection methods to assess feasibility and acceptability before embarking on the development of additional features of the ePRO module. However, this is a double-edged sword when it comes to the ultimate goal of integrating PROs into routine care. While we avoided running the risk of prolonging regulatory approvals and delaying the pilot study, we have also delayed providing feedback to providers. A priority area of action and future research is grappling with and overcoming the regulatory issues associated with displaying either aggregated or individual patient-reported data and working with clinicians and patients to develop care protocols based on patient-generated/reported data.

Confidentiality

Participants had to have a personal e-mail address and a reliable Internet connection in order to use the ePRO module. We decided to use an e-mail address for the account creation process to stimulate a new form of engagement with the ANRS CO3 Aquitaine cohort. This conscious choice is also reflected in the choice of language on the study documents, which emphasises patients as partners in research and ultimately care. While we were careful to specify that e-mail addresses would be stored separately and opted for neutral colours (e.g. dark pink versus red) and anonymity on the study documents, this strategy was a gamble. One of the ongoing concerns is the relatively low registration rate in spite of the QuAliV's initiative being generally well-received. One of the first hypothesized reasons was confidentiality. In other words, just because someone has an e-mail address does not mean that he/she wishes for it to be linked to an ongoing study on HIV. But, to date, only a handful of the 1,732 PLWH seen during the study's initial implementation refused to participate or opted for a paper questionnaire for this reason. Nevertheless, we do not know how many people visited the study's website and opted not to continue upon seeing and taking stock of the account creation process (requiring one to enter his/her e-mail address).

We found that the majority of those approached were interested in the initiative and met the basic requirements to use the ePROs solutions. However, "having an e-mail address" does not mean that one is necessarily comfortable setting-up one's account independently. The formative research phase proved critical in shedding light on how PLWH interacted with the proposed ePRO module. As highlighted in chapter 2, the account creation was the most challenging "task" in the usability evaluation. We assumed that overall usefulness of interactive health care applications or their usability is likely to affect their acceptability and adoption. However, formative research and time spent shadowing physicians during

the initial implementation of the study at the St André hospital elucidated other impediments to use, e.g. not recalling one's e-mail account password when using a borrowed computer or not having one's reading glasses at the hospital. We intend to improve registration among eligible participants by reminding them to create their account at the next consultation and asking them to complete the initial baseline assessment. We presume that Smartphone use is higher than regular e-mail use in this population. The second strategy that is planned is to allow for account creation using one's phone number. If participants consent, reminders to complete assessments can then be sent via SMS.

Choice of instrument

We based the decision about which instruments to include on both previous research on factors associated with quality of life and current recommendations for ongoing care for HIV and its associated comorbidities. As addressed in the introduction, we were confronted with the choice of which instrument to select when it came to measuring QoL given the numerous options. I made recommendations to the Steering Committee based on the conclusions of different systematic reviews [51] followed by an examination of the instruments' content validity. The MOS-HIV, comprising 35 items and covering 10 dimensions, was originally considered for use as it had extensive documentation of its psychometric properties [57, 58]. However, upon closer inspection of the MOS-HIV's items, we questioned whether it would be appropriate in a population where more than 90% of people were virally-suppressed. We turned to newer instruments, namely the PROQOL-HIV and the WHOQOL-HIV BREF, which had been developed with input from PLWH in different countries. This approach is intended to produce global concepts, items and protocols and reduce equivalence problems. That said, these instruments (PROQOL-HIV and WHOQOL-HIV BREF), although "newer", are based on items which were generated from qualitative research conducted in the mid-2000s in the global north and south prior to current universal treatment guidelines.

We decided to include the WHOQOL-HIV BREF instrument in our battery of PROs. According to the WHO, the first four domains, relating to (i) physical health, (ii) psychological health, (iii) level of independence, (iv) social relations, are more likely directly affected by health and the use of medicines and healthcare technology, whereas the last two domains (environment and personal values and beliefs), although important, may not be as frequently affected by the use of health care (including medicines**).** The WHOQOL-HIV BREF's broad conceptualisation of quality of life, going beyond physical and mental health, is of value in a population of stable PLWH who are doing well on ART. However, unlike other HRQoL instruments, a global or summary physical/mental health scores are not produced, making it potentially less accessible to a non-specialist user and its analysis more complex. On the other hand,

this feature can be seen as an advantage, drawing attention to the latent traits or factors comprising multi-dimensional quality of life. Our initial findings regarding the instrument's measurement properties suggest that several of the participants responses cluster towards the high end (or best possible score) for the measurement/instrument for several HIV-specific items. Subsequent analyses of these HRQoL will have to take into account this finding.

The constraints of academic research versus the pragmatic needs of IT development

The successful implementation of this study hinged on an ePROs module being developed in house to facilitate the long-term collection of PROs within the ANRS CO3 Aquitaine cohort. As we were implementing this study within a public university setting, it was somewhat challenging to apply standard commercial software development practices. For example, agile software development favours iterative and incremental methods and focuses on process adaptability and customer satisfaction by rapidly delivering working software products. In contrast, academic research seeks to produce evidence regarding the development and adaptation of IT solutions and workflows for academic publications and dissemination. We were somewhat challenged in this respect as we lacked the human resources to undertake more agile software development. This resulted in pragmatic temporary solutions being adopted to facilitate the study's implementation. This tension between best IT development practices and the demands of academia has been noted by others [113]. Mann and colleagues have suggested that hybrid digital development processes be adopted to balance the needs of research and those of IT development.

Involvement of end-users

There is no doubt that PLWH have been trailblazers when it comes to advocating for greater involvement of patients (or rather PLWH) at every level of decision-making. The Denver Principles of 1983 are often cited as having profoundly influenced the role of patient organisations within the health system. In line with these principles, we have made substantial efforts to involve and incorporate the views of end users throughout the process of conceiving of and implementing this study. We did this by involving a local patient representative from the association AIDES in the study's Steering Committee. The study documents (including the content of the questionnaire) were also shared with members of the European AIDS Treatment Group. PLWH seen in care were also involved in evaluating the ePRO module's usability. Future IT development efforts must place the user at the centre of the innovation process. We must approach these projects not only from a public health or health system's innovation perspective,

basing our choice of instruments on our understanding of modifiable risk factors, but also take into consideration patients' preferences. It will be important to draw on co-design research techniques [114] and those employed by Living Labs. These spaces and new methods have been taken up by those addressing other chronic illnesses like diabetes or loss of independence in the elderly or the handicapped. Furthermore, it will likely be important to identify motivated partners who are willing to engage in user-cantered design to ensure a thorough understanding of the needs, wants and limitations of the end user (be they physicians or PLWH). It will also be critical to consider the heterogeneity among departments, physicians (in terms of workflow) and patients as we expand upon the proposed features.

Timing of the PROs assessments in the context of chronic disease management

As we move forward, one of the main questions is the optimal or sensible timing of PROs assessments in a population of patients receiving ongoing chronic disease care. This issue is compounded by the fact that the ANRS CO3 Aquitaine cohort is an open, prospective, hospital-based cohort study based on patients' routinely collected clinical and biological data. Unlike an interval cohort where study visits are planned, potentially providing a perfect opportunity to incorporate a PROs assessment, participants do not attend study-specific consultations or blood draws. Crane and colleagues who have experimented with the collection of PROs in several different clinical settings in the United States speak to the need to prioritise the collection of PROs in the organisation of care. In some clinics, patients are scheduled to come in earlier and given a 15-minute window to complete PROs and other assessments prior to the HIV consultation. In others, PROs assessments are completed as patients wait to be seen by HIV care providers. In the context of HIV care, the regularity of visits may also vary depending on the patient's care needs. Should patients be invited to complete an assessment every time he/she is seen for HIV care? Should this be done in the week or days prior to the consultation in the case of a "Bring Your Own Device Solution"? Should they be linked to an annual check-up or should every hospital contact be seen as opportunity for screening, prevention and optimised management of ongoing care? Crane and colleagues have proposed having PROs assessments completed at every hospital contact, making them truly a routine part of care and a default for administrative staff. She suggests that an opt-out rule could be adopted for those being seen more regularly for an acute issue. For example, if the patient had completed an assessment within three months of the consultation, he/she would be exempt from the PROs assessment. However, a different approach has been taken by ComPaRe, an e-epidemiology research platform focused on collecting PROs on a regular basis from people with a chronic illness in France. Those who have signed up to be part of ComPaRe complete an assessment (lasting up to an hour but from home) as often as once a month for use for research.

The digital divide in the context of care and services for PLWH

The population of PLWH in France is a heterogeneous group, reflecting the epidemic's history. People most affected by HIV are from what we have come to refer to as "key populations" or those who experience structural violence (stigma and discrimination, restrictive laws and policies, and criminalisation of behaviours and practices), putting them at greater risk of contracting HIV compared to the general population and preventing them from accessing health services. Key populations refer to MSM, Transgender people, Sex workers, people who inject drugs and those in prison. Migrants (some of whom are also represented within key populations) also make up a large share of those living with HIV in Western Europe, including France [115]. Poor socioeconomic and living conditions, together with language, cultural and legal barriers put them at higher risk for contracting HIV [116] and for suboptimal outcomes [117]. These realities imply that the use of Information and Communication Technologies (ITC) in PLWH should be approached with some caution so as to not widen the digital divide or the uneven distribution in access to, use of, or impact of ICT between a number of distinct groups. Conscious of this issue, we devised a paper questionnaire as a back-up option for those who did not meet the basic requirements of the ePRO's system. This approach appears to have helped to minimise the potential selection bias or ultimately "e-exclusion" that could have been created with an exclusively electronic data collection approach. We had no idea what proportion of participants would meet the basic requirements of the ePRO module. To our surprise, this figure appears to be relatively high, estimated to be 80-82% at present, with some variability observed according to hospital. As evidenced in the analyses of initial acceptability, presented in chapter three, those who opted for the paper version of the questionnaire (18-20% of those who agreed to participate) were either older or more socio-economically disadvantaged.

New models of or differentiated HIV care

Lifestyle-associated and conventional risk factors now account for a substantial and potentially preventable part of the burden of age-related diseases in PLWH. Primary and secondary prevention of co-infections and co-morbidities is now a pillar of long-term HIV care. As with other chronic diseases, there is a strong incentive to decentralize and better coordinate hospital-based and ambulatory care. The Haute Autorité de Santé's recent guidance for general and hospital practitioners is the first effort to establish this partnership. We do not know, however, what the real world implications will be in terms of healthcare trajectories, utilisation, costs and outcomes. There is no guarantee that "shared" follow-up is more cost-effective. We intend to estimate the value provided to those living with HIV in care (measured with PROs) in relation to the costs of providing care from the perspective of the provider

(measured with administrative data from the French health system) in order to reflect on current models of health care delivery and inform the development of future models of care.

As evoked in the discussion of chapter 1, the panel of services provided via the proposed ePRO system could ultimately be expanded. For example, continuous patient education/coaching for better self-management, similar to interventions that have been implemented for other chronic conditions (diabetes, heart disease, etc), could be offered, as could decentralized models of care and/or facilitated communication with one's general practitioner. The acceptability, adoption, relevance, feasibility, fidelity of innovations designed to promote better health-related quality of life (e.g. self-management applications) could ultimately be the aim of future experimental research in this patient population aging with HIV. Alternatively, the proposed system, designed for outpatient hospital-based HIV care, could be adapted for use in other chronic diseases and/or other care settings.

Conclusion

PROs have a role to play in informing the evolving HIV care paradigm. Yet, ensuring that they are integrated into hospital-based HIV care successfully will require further experimentation. The QuAliV study has been the first step in fostering a new relationship with those in care in the region. It has resulted in highlighting a number of areas that we feel need to be addressed in order to successfully develop new value-based models of care/social services which take into consideration and efficiently respond to PLWH's global needs.

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Annex I : Study Document : Pre-inclusion sheet

Fiche de liaison

QuAliV– CHUBX2016/14

Version 1.0

N° QuAliV | | | | | | | | |

À compléter par l'investigateur

DATE | | | | | | | | | | |

Jour *Mois* *Année*

Information donnée au participant ☐ oui ☐ non

Eligible pour la version électronique du questionnaire : ☐ oui ☐ non

Si non, proposition de la version papier du questionnaire : ☐ oui ☐ non

Statut à la fin de la consultation :

☐ Accepté
(version électronique ou papier)

☐ Refusé

☐ Non éligible
(ex. non francophone, autres raisons)

Raison(s) de refus ou de non éligibilité

Annex II : Study Document : Study Poster

Annex III : Study Document : Study-specific brochure

REJOIGNEZ UNE NOUVELLE COMMUNAUTÉ DE PARTICIPANTS À LA RECHERCHE

QuAliV est une étude scientifique de la cohorte ANRS CO3 Aquitaine.

Il s'agit d'une nouvelle démarche qui cherche à repenser votre prise en charge en vous impliquant plus directement.

QuAliV

TITRE DE L'ÉTUDE
Qualité de vie des personnes vivant avec le VIH en Aquitaine : mesure, déterminants et axes de prise en charge

ACRONYME
QuAliV

CODE PROMOTEUR
CHUBX2016/04

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COORDONNATEUR DE L'ÉTUDE
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NOS PARTENAIRES

CHU Bordeaux · ANRS · Inserm · Sidaction · université de BORDEAUX · COREVIH Nouvelle-Aquitaine

QuAliV

Ensemble,
améliorons votre qualité de vie

QuAliV est une étude scientifique sur la **qualité de vie** des personnes vivant avec le **VIH**

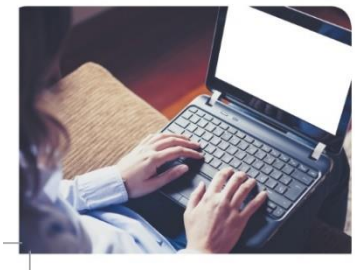
Rejoignez-nous sur **qualiv.fr**
pour en savoir plus et participer !

POURQUOI PARTICIPER ?

Vous participez actuellement à la cohorte ANRS CO3 Aquitaine des personnes vivant avec le VIH dans la région. La recherche sur votre évolution clinique et vos résultats biologiques a déjà permis de faire avancer nos connaissances sur le VIH et d'améliorer sa prise en charge.

Maintenant, l'étude QuAliV vous invite à vous impliquer plus directement dans la connaissance et l'analyse de votre situation personnelle : conditions de vie, habitudes, humeur et les différents aspects de la qualité de vie et de la prise en charge.

Nous, soignants et chercheurs, espérons ainsi mieux répondre à vos besoins d'aujourd'hui et de demain afin d'améliorer votre qualité de vie.



COMMENT PARTICIPER ?

Pour participer, votre médecin va vous poser quelques questions afin de s'assurer que votre situation correspond bien aux critères d'éligibilité de l'étude. Il vous remettra un numéro personnalisé avec lequel vous pourrez créer votre compte sur le site Internet **qualiv.fr** afin de remplir le premier questionnaire.

Ensuite, chaque année, nous vous demanderons de répondre en ligne en quelques questions sur comment vous vous portez.

Toutes les informations que vous communiquerez resteront rigoureusement et strictement confidentielles.

Si vous ne disposez pas une adresse courriel ou un accès Internet, vous pouvez toujours participer !

Demandez à votre médecin de vous fournir une version papier du questionnaire que vous pourrez remplir sur place.

QU'EST-CE QUE J'Y GAGNE ?

EN PARTICIPANT À QUALIV :

- Vous contribuerez à une grande étude scientifique soutenue par les instituts de recherche médicale en France
- Vous permettrez une amélioration des connaissances scientifiques pour l'ensemble des personnes vivant avec le VIH !
- Vous en tirerez aussi un bénéfice individuel. En accédant à vos réponses, votre médecin pourra mieux répondre à vos besoins et ainsi améliorer votre état de santé.

COUPON À CONSERVER :

Rejoindrez-nous sur le site **qualiv.fr** muni de votre numéro personnalisé pour vous inscrire et remplir le premier questionnaire !

NUMÉRO PERSONNALISÉ :

MÉDECIN INVESTIGATEUR À CONTACTER EN CAS DE QUESTIONS :

Annex IV : Study Document: Non-opposition or tacit agreement letter

Information du participant et vérification de sa non-opposition (version papier)

QuAliV : Qualité de vie liée à la santé des personnes vivant avec le VIH en Aquitaine : mesure, déterminants et axes de prise en charge

« QuAliV » - CHUBX2016/04

Gestionnaire de la recherche : CHU de Bordeaux
Personne qui dirige et surveille la recherche : Pr Fabrice BONNET

Madame, Monsieur,

Vous avez accepté de participer à une cohorte de personnes vivant avec le VIH (PVVIH) dans la région Nouvelle Aquitaine (la Cohorte ANRS CO3 Aquitaine). L'étude de votre évolution clinique et de vos résultats biologiques a déjà permis de faire avancer nos connaissances sur le VIH et par conséquent d'améliorer sa prise en charge. Grâce aux traitements disponibles aujourd'hui, l'infection par le VIH est considérée comme une maladie chronique. Bien qu'elles aient évolué ces dernières années, des problématiques persistent et peuvent affecter votre qualité de votre vie. Pour mieux répondre à vos besoins et continuer à améliorer votre état de santé global, nous devons essayer de mieux comprendre votre quotidien et votre environnement (conditions de vie, habitudes, qualité de vie, prise en charge, humeur, qualité de vie sexuelle).

QuAliV est un projet scientifique de la cohorte ANRS CO3 Aquitaine qui vise à mieux comprendre l'état de santé global de ceux qui vivent avec le VIH, en les impliquant plus directement dans la connaissance et l'analyse de leur situation personnelle afin, à terme, de proposer des solutions pratiques.

Après avoir lu la note d'information, vous serez invité à compléter le premier questionnaire comprenant plusieurs modules. Toutes les informations que vous communiquerez resteront rigoureusement et strictement confidentielles. A cette fin, les données médicales vous concernant et les données relatives à vos habitudes de vie, ainsi que, dans la mesure où ces données sont nécessaires à la recherche, les données relatives à votre vie sexuelle, seront transmises au CHU de Bordeaux ou aux personnes ou sociétés agissant pour son compte, en France ou à l'étranger. Nous nous réservons le droit de vous recontacter pour vous signaler que votre questionnaire n'a pas été terminé ou pour compléter ce bilan. Une partie ou la totalité de vos données pourra, sauf opposition de votre part, être conservée et utilisée pour des recherches dans le respect de la confidentialité. Ces données seront identifiées par un code, et ne permettront pas de vous identifier notamment par vos nom et prénom qui ne sont recueillis que pour le suivi de l'étude et non dans le cadre de la recherche. Les données rendues confidentielles pourront être utilisées pour des recherches effectuées en partenariat avec un ou plusieurs organismes publics ou privés.

Votre participation à cette recherche est entièrement volontaire et vous avez le droit de vous opposer à y participer. Dans ce cas-là, vous continuerez à bénéficier de la meilleure prise en charge médicale possible, conformément aux connaissances actuelles.

Conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, vous disposez à tout moment d'un droit d'accès et de rectification des données informatisées vous concernant (loi n° 2004-801 du 6 août 2004 modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés). Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de ces recherches et d'être traitées. Vous pouvez également accéder directement ou par l'intermédiaire du médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L1111-7 du code de la santé publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.

Après avoir lu cette note d'information, n'hésitez pas à poser au médecin investigateur toutes les questions que vous désirez. Une fois complété, un exemplaire du document vous sera remis.

Cadre réservé au service

Nom du participant : ……..

Date d'information : le ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

Opposition exprimée : ☐ oui ☐ non

Nom de la personne responsable de la recherche : ……..

Signature de la personne responsable de la recherche :

Placer l'original dans le dossier du participant, remettre une copie au participant.

Annex V: Study Document : Paper self-administered questionnaire

COMMENT REMPLIR CE QUESTIONNAIRE ?

Pour la plupart des questions, vous trouverez des petites cases. Vous répondez en faisant une croix dans une case. Si vous hésitez, choisissez celle qui vous semble la plus proche et la plus appropriée à ce que vous ressentez ou vivez.

Exemple

	Pas du tout	Un peu	Modérément	Beaucoup	Extrêmement
Êtes-vous satisfait de votre santé ?	☐ 1	☒ 2	☐ 3	☐ 4	☐ 5

Une fois que vous avez terminé de remplir ce questionnaire, remettez-le à votre médecin ou au secrétariat de son service.

Les questions suivantes portent sur votre situation sociale et économique. **Répondez à toutes les questions s'il vous plaît**.

Date d'aujourd'hui ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋
jour mois année

1.1. Vous êtes ?

- ☐ Un homme
- ☐ Une femme
- ☐ Un homme devenu femme
- ☐ Une femme devenue homme

1.2. Quelle est votre date de naissance ? ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋
jour mois année

1.3. Quel est le code postal de votre domicile ? ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

1.4. Quel est votre niveau d'études le plus élevé ?

- ☐ Aucun diplôme
- ☐ Certificat d'études primaires
- ☐ Brevet
- ☐ CAP, BEP ou équivalent
- ☐ Baccalauréat, Brevet professionnel ou équivalent
- ☐ Baccalauréat +2
- ☐ Baccalauréat +3
- ☐ Baccalauréat +5 ou plus
- ☐ Ne sait pas

1.5. Quelle est votre situation professionnelle aujourd'hui ? *plusieurs réponses sont possibles*

- ☐ Etudiant
- ☐ En emploi à temps plein
- ☐ En emploi à temps partiel
- ☐ En apprentissage sous contrat ou en stage rémunéré
- ☐ Au chômage (inscrit ou non au Pôle Emploi, percevant ou non des allocations)
  Depuis combien de temps ? :.....mois
- ☐ En formation avec un soutien du Pôle Emploi
- ☐ Retraité ou préretraité
- ☐ Sans emploi ou inactif

1.6. Quelle est votre profession (ou la dernière profession que vous ayez exercée) ?

- ☐ Ouvriers
- ☐ Agriculteurs exploitants
- ☐ Artisans, commerçants et chefs d'entreprise
- ☐ Cadres et professions intellectuelles supérieures ou libérales
- ☐ Profession intermédiaire
- ☐ Employés
- ☐ Ne souhaite pas répondre

1.7. **Bénéficiez-vous d'une assurance maladie complémentaire, une mutuelle ou de la protection universelle maladie (anciennement CMU-C) ?**

☐ Oui ☐ Non ☐ Ne sait pas

1.8. **De combien sont les revenus globaux nets de votre ménage* par mois (y compris les allocations familiales et/ou la pension alimentaire) ?**

** par ménage, nous entendons toutes les personnes qui habitent le même logement que le vôtre*

☐ Moins de 900 €
☐ De 900 à 1499 €
☐ De 1500 à 2000 €
☐ De 2001 à 3000 €
☐ De 3001 à 4000 €
☐ Plus de 4000 €
☐ Ne souhaite pas répondre

1.9. **Y-a-t-il des périodes dans le mois où vous rencontrez de réelles difficultés financières pour faire face à vos besoins (alimentation, loyer, électricité...) ?**

☐ oui ☐ non

1.10. **En cas de difficultés, y-a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous héberger quelques jours ?**

☐ oui ☐ non

1.11. **Bénéficiez-vous d'un ou plusieurs des minima sociaux (ex. RSA ou AAH) ?**

☐ oui ☐ non

→ Si oui, lesquels ? *plusieurs réponses sont possibles*

☐ Allocation équivalent retraite (AER)
☐ Revenu de solidarité active (RSA)
☐ Allocation aux adultes handicapés (AAH)
☐ Allocation de solidarité aux personnes âgées (ASPA)
☐ Allocation de solidarité spécifique (ASS)
☐ Allocation veuvage (AV)
☐ Allocation pour les demandeurs d'asile (ADA)
☐ Allocation supplémentaire d'invalidité (ASI)
☐ Prime transitoire de solidarité (PTS)
☐ Allocation temporaire d'attente (ATA)
☐ Autre
☐ Ne sait pas

1.12. **Vivez-vous en couple ?**

☐ oui ☐ non

1.13. **Combien votre ménage* compte-t-il de personnes ?** *indiquez la réponse en chiffre*

**Par ménage, nous entendons toutes les personnes qui partagent le même logement que le vôtre.*

Adultes (y compris vous)	Enfant de plus 16 ans	Enfant de moins de 16 ans
⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌋

1.14. Bénéficiez-vous des allocations familiales ?

☐ oui ☐ non

1.15. Au cours des 6 derniers mois, avez-vous eu des contacts avec des membres de votre famille, autres que vos parents ou vos enfants ?

☐ oui ☐ non

1.16. Actuellement vous vivez ?

☐ Dans un logement dont vous êtes le propriétaire
☐ Dans un logement dont vous êtes locataire
☐ Dans un logement à caractère social (ex. HLM)
☐ Chez vos parents ou chez un membre de votre famille
☐ Chez des amis
☐ Dans un foyer ou un centre d'hébergement (CHRS, foyer pour jeunes travailleurs, foyer de travailleurs immigrés etc.)
☐ À l'hôtel
☐ Sans domicile
☐ Autres

→ Bénéficiez-vous des aides personnalisées au logement (les APL) ?

☐ oui ☐ non

→ Si oui, lesquelles ?

☐ Aide personnalisée au logement (APL) ☐ Allocation de logement à caractère familial (ALF) ☐ Ne sait pas

1.17. Rencontrez-vous parfois un travailleur social ?

☐ oui ☐ non

1.18. Êtes-vous parti en vacances au cours des 12 derniers mois ?

☐ oui ☐ non

1.19. Êtes-vous allé à un spectacle au cours des 12 derniers mois ?

☐ oui ☐ non

1.20. Vous est-il arrivé de faire du sport au cours des 12 derniers mois ?

☐ oui ☐ non

Ces questions visent à évaluer votre qualité de vie et votre ressenti par rapport à votre santé et aux autres domaines de votre vie. **Vous devez répondre à toutes les questions**.

Si vous hésitez entre plusieurs réponses, choisissez celle qui vous semble la plus appropriée. Il s'agit souvent de votre premier choix.

Gardez bien à l'esprit vos idées, vos attentes, vos plaisirs. Nous attendons que vous vous basiez sur votre vie au cours **des deux dernières semaines** pour répondre.

Exemple : en se basant sur les deux dernières semaines, une question pourrait être :

	Pas du tout	Un peu	Modérément	Beaucoup	Extrêmement
Arrivez-vous à vous concentrer facilement ?	☐ 1	☒ 2	☐ 3	☐ 4	☐ 5

Vous devrez cocher la case associée à la réponse qui correspond le mieux à l'intensité avec laquelle vous estimez arriver à vous concentrer pendant les **deux dernières semaines**.

Au cours **des deux dernières semaines** :

	Très faible	Faible	Ni faible, ni bonne	Bonne	Très bonne
2.1. **Comment évaluez-vous votre qualité de vie ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Très insatisfait	Insatisfait	Ni insatisfait, ni satisfait	Satisfait	Très satisfait
2.2. **Êtes-vous satisfait de votre santé ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Les questions suivantes portent sur la manière dont vous avez ressenti certaines situations au cours des **deux dernières semaines**.

		Pas du tout	Un peu	Modérément	Beaucoup	Extrêmement
2.3.	**La douleur physique vous empêche-t-elle de faire ce dont vous avez envie ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.4.	**Dans quelle mesure, êtes-vous tracassé par tout problème physique lié à votre infection par le VIH ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.5.	**Un traitement médical vous est-il nécessaire pour faire face à la vie de tous les jours ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.6.	**Trouvez-vous votre vie agréable ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.7.	**Estimez-vous que votre vie a du sens ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.8.	**Êtes-vous affecté par les reproches des personnes autour de vous par rapport au VIH ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.9.	**Avez-vous peur de l'avenir ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.10.	**Êtes-vous inquiet par rapport à la mort ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.11.	**Êtes-vous capable de vous concentrer ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.12.	**Vous sentez-vous en sécurité dans votre vie quotidienne ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.13.	**Vivez-vous dans un environnement sain ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Les questions suivantes visent à évaluer dans quelle mesure vous avez vécu ou été capable de faire certaines choses de manière complète au cours des **deux dernières semaines**.

		Pas du tout	Un peu	Modérément	Beaucoup	Extrêmement / Complètement
2.14.	**Avez-vous assez d'énergie dans votre vie quotidienne ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.15.	**Acceptez-vous votre apparence physique ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.16.	**Avez-vous assez d'argent pour satisfaire vos besoins ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.17.	**Vous sentez-vous accepté par votre entourage ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.18.	**Avez-vous le sentiment d'être assez informé pour faire face à la vie de tous les jours ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.19.	**Avez-vous l'occasion de pratiquer des loisirs ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		Très mal	Mal	Ni mal, ni bien	Bien	Très bien
2.20.	**Comment arrivez-vous à vous déplacer ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Les questions suivantes portent sur la manière dont vous avez été satisfait, heureux par rapport aux différents aspects de votre vie au cours des **deux dernières semaines**.

	Très insatisfait	Insatisfait	Ni insatisfait, ni satisfait	Satisfait	Très satisfait
2.21. **Êtes-vous satisfait de votre sommeil ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.22. **Êtes-vous satisfait de votre capacité à effectuer les tâches de la vie quotidienne ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.23. **Êtes-vous satisfait de votre capacité à travailler?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.24. **Êtes-vous satisfait de vous ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.25. **Êtes-vous satisfait de vos relations avec les autres ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.26. **Êtes-vous satisfait de votre vie sexuelle ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.27. **Êtes-vous satisfait du soutien de vos amis ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.28. **Êtes-vous satisfait avec votre lieu de vie ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.29. **Êtes-vous satisfait de l'accès aux services de santé ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.30. **Êtes-vous satisfait de vos moyens de transport ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

La question suivante se rapporte à la fréquence avec laquelle vous avez ressenti ou vécu certaines choses pendant les **deux dernières semaines**.

	Jamais	Rarement	Assez souvent	Très souvent	Tout le temps
2.31. **Avez-vous des sentiments négatifs tels que de la mélancolie, du désespoir, de la dépression, de l'anxiété ?**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Les questions suivantes portent sur votre traitement dans son ensemble. Veuillez cocher la case qui vous semble la plus représentative de votre situation. **Répondez à toutes les questions s'il vous plaît**.

3.1. Concernant la prise de vos médicaments, comment évalueriez-vous les contraintes liées :

Au **goût**, à la **forme**, à la **taille de vos comprimés** et aux **désagréments causés par vos injections** (douleur, saignements, séquelles inesthétiques…) ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Au **nombre de fois** où vous devez prendre vos médicaments par jour ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Aux efforts que vous devez faire pour **ne pas oublier de prendre vos médicaments**, vous organiser pendant vos voyages, utiliser un pilulier… ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Aux **précautions d'emploi** de vos médicaments (devoir prendre les médicaments à un moment précis de la journée ou du repas ; ne pas pouvoir faire certaines choses après les avoir pris comme s'allonger ou conduire…) ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Aux précautions que vous devez prendre **pour conserver** vos médicaments (au froid dans votre réfrigérateur…) ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable

3.2. Concernant la surveillance de votre maladie, comment évalueriez-vous les contraintes liées :

Aux **examens complémentaires** (analyses de sang, examens radiologiques...) : au **nombre**, au **temps consacré** et à la **pénibilité** de ces examens ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
A la **surveillance que vous réalisez vous-même** (mesurer votre tension à domicile, faire des glycémies capillaires, tenir un carnet de suivi...) : à la **fréquence**, au **temps consacré** et à la **pénibilité** de cette surveillance ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Aux **visites chez vos médecins** : au **nombre** et au **temps consacré** à ces consultations ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
A **la prise de rendez-vous** médicaux (visites chez vos médecins, analyses de sang, autres examens...) et l'**organisation de votre emploi du temps** à cause de ces rendez-vous ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable

3.3. Comment évalueriez-vous :

Les contraintes administratives liées à votre maladie (formalités liées aux hospitalisations, aux remboursements par l'Assurance Maladie, aux démarches sociales...) ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Les contraintes financières liés à votre maladie (par exemple : prises en charge ou traitements non remboursées...) ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Les contraintes liées à **votre régime** (éviter certains aliments, s'alimenter avec un minimum de calories au moment des prises...) ?											
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable

La contrainte que représentent les recommandations de vos médecins pour **faire des activités physiques** (marche, course, natation…) ?												
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
Quel impact votre traitement a-t-il sur **vos relations avec les autres** (avoir besoin d'être aidé dans la vie de tous les jours, avoir honte de prendre vos médicaments, ne pas révéler son statut sérologique…) ?												
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable
« Le fait de me soigner régulièrement **me rappelle que je suis malade**. »												
☐ Je ne suis pas concerné	Aucun impact	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Impact considérable

Si d'autres aspects de votre prise en charge peuvent représenter une contrainte pour vous et ne figurent pas dans les questions ci-dessus, merci de les indiquer ici.

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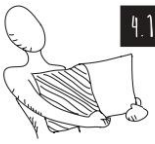
QUESTIONNAIRE 4 :

MON MODE DE VIE

Nous nous intéressons aux différents types d'activités physiques que vous faites dans votre vie quotidienne. Les questions suivantes portent sur le temps que vous avez passé à être actif physiquement au cours des **7 derniers jours**.

Répondez à chacune de ces questions même si vous ne vous considérez pas comme une personne active. Les questions concernent les activités physiques que vous faites au travail, lorsque vous êtes chez vous, lors de vos déplacements et pendant votre temps libre.



4.1. Pensez à toutes les activités intenses que vous avez faites au cours des **7 derniers jours**.

Les activités physiques intenses font référence aux activités qui vous demandent un effort physique important et vous font respirer beaucoup plus difficilement que normalement. Pensez seulement aux activités que vous avez fait sur une durée d'au moins 10 minutes d'affilée.

Dans les 7 derniers jours, quel est le nombre de jours au cours desquels vous avez fait des activités physiques intenses telles que porter des charges lourdes, bêcher, faire du VTT, de la natation ou jouer au football ?

└┘ jour(s) ☐ Je n'ai pas eu d'activité physique intense.
[Passez à la question suivante]

Au total, combien de temps avez-vous consacré à des activités intenses au cours des 7 derniers jours ?

└┘└┘ heure(s) └┘└┘ minute(s)

4.2. Pensez à toutes les activités modérées que vous avez faites au cours des **7 derniers jours**.

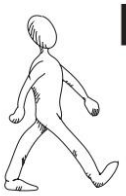
Les activités physiques modérées font référence aux activités qui vous demandent un effort physique modéré et vous font respirer un peu plus difficilement que normalement. Pensez seulement aux activités que vous avez fait sur une durée d'au moins 10 minutes (ex. marche rapide, gymnastique ou yoga, tondre la pelouse).

Dans les 7 derniers jours, quel est le nombre de jours au cours desquels vous avez fait des activités physiques modérées telles que porter des charges légères, passer l'aspirateur, faire du vélo tranquillement ou jouer au volley-ball ? Ne pas inclure la marche.

└┘ jour(s) ☐ Je n'ai pas eu d'activité physique intense.
[Passez à la question suivante]

Au total, combien de temps avez-vous consacré à des activités modérées au cours des 7 derniers jours ?

└┘└┘ heure(s) └┘└┘ minute(s)



4.3. Pensez au temps que vous avez passé à marcher pendant **au moins 10 minutes** au cours des **7 derniers jours**.

Cela comprend la marche au travail et à la maison, la marche pour vous rendre d'un lieu à un autre, et tout autre type de marche que vous auriez pu faire pendant votre temps libre pour la détente, le sport ou les loisirs.

Dans les 7 derniers jours, quel est le nombre de jours au cours desquels vous avez marché sans vous arrêter pendant au moins 10 minutes ?

☐☐ jour(s) ☐ Je n'ai pas fait de marche

Au total, combien d'épisodes de marche d'une durée d'au moins 10 minutes, avez-vous effectués au cours des 7 derniers jours ?

☐☐☐☐ nombre d'épisodes de 10 minutes d'affilée ☐ Je ne sais pas

Exemples :

Lundi :	*1 marche de 60 minutes*	*6 épisodes*
Mardi :	*1 marche de 20 minutes et 3 marches de 5 minutes*	*2 épisodes*
Mercredi :	*1 marche de 35 minutes*	*3 épisodes*
Jeudi :	*1 marche de 8 minutes*	*0 épisode*
Vendredi :	*1 marche de 6 minutes puis 3 marches de 4 minutes*	*0 épisode*
Samedi :	*1 marche de 18 minutes*	*1 épisode*
Dimanche :	*1 marche de 10 minutes et 3 marches de 5 minutes*	*1 épisode*
	Total	*13 épisodes*

Les questions suivantes portent sur vos habitudes de consommation d'alcool.

4.4. **À quelle fréquence vous arrive-t-il de consommer une boisson contenant de l'alcool ?**

Jamais	Une fois par mois ou moins	2 à 4 fois par mois	2 à 3 fois par semaine	Au moins 4 fois par semaine
☐ *[Passez à la question 4.10.]*	☐	☐	☐	☐

4.5. **Combien de verres standard* buvez-vous au cours d'une journée ordinaire où vous buvez de l'alcool ?**

** Verre standard est égal à 10 grammes d'alcool pur soit : 10 cl de vin à 12°, 25 cl de boissons à 5° (bière, sodas alcoolisés [alcopops – prémix]), 7 cl de vin cuit à 18°, 3 cl d'alcool à 40° (whisky, pastis ou digestif).*

1 ou 2	3 ou 4	5 ou 6	7 à 9	10 ou plus
☐	☐	☐	☐	☐

4.6. **À quelle fréquence vous arrive-t-il de boire six verres standard* ou davantage lors d'une occasion particulière (ex. fête de famille, sorties, repas) ?**

Jamais	Moins d'une fois par mois	Une fois par mois	Une fois par semaine	Tous les jours ou presque
☐	☐	☐	☐	☐

4.7. **Est-ce que votre entourage vous a fait des remarques concernant votre consommation d'alcool ?**

☐ oui ☐ non

4.8. **Vous est-il arrivé de consommer de l'alcool le matin pour vous sentir en forme ?**

☐ oui ☐ non

4.9. **Vous est-il arrivé de boire et de ne pas vous souvenir le matin de ce que vous avez pu dire ou faire ?**

☐ oui ☐ non

Les questions suivantes portent sur vos habitudes vis-à-vis du tabac et de la nicotine.

4.10. Êtes-vous fumeur ?

- ☐ Oui, je fume tous les jours.
- ☐ Oui, je fume, mais pas tous les jours.
- ☐ Non, mais auparavant je fumais tous les jours.
- ☐ Non, je n'ai jamais fumé. *[Passez à la question 4.11]*

→ Combien de temps après votre réveil fumez-vous votre première cigarette ?

☐ Dans les 5 premières minutes ☐ Entre 6 et 30 minutes ☐ Entre 31 et 60 minutes ☐ Après 60 minutes

→ Trouvez-vous difficile de vous abstenir de fumer dans les endroits où cela est interdit (ex. cinémas, bibliothèques, transports) ?

☐ oui ☐ non

→ À quelle cigarette de la journée renonceriez-vous le plus difficilement ?

☐ La première le matin ☐ N'importe quelle autre

→ Combien de cigarettes fumez-vous par jour en moyenne ?

☐ 10 ou moins ☐ 11 à 20 ☐ 21 à 30 ☐ 31 ou plus

→ Fumez-vous à intervalles plus rapprochés durant les premières heures de la matinée que durant le reste de la journée ?

☐ oui ☐ non

→ Fumez-vous lorsque vous êtes malade au point de devoir rester au lit presque toute la journée ?

☐ oui ☐ non

→ Avez-vous déjà essayé d'arrêter de fumer ? *[Passez à la question 4.11]*

☐ oui ☐ non

→ À quel âge avez-vous fumé pour la première fois ?

☐☐ ans

Lorsque vous fumiez, combien de cigarettes consommiez-vous par jour en moyenne ?

☐ 10 ou moins ☐ 11 à 20 ☐ 21 à 30 ☐ 31 ou plus

Depuis combien de temps avez-vous arrêté de fumer ?

☐☐ ans

4.11. Avez-vous déjà essayé la cigarette électronique ?

☐ oui ☐ non *[Passez à la question 4.12]*

→ Quel âge aviez-vous lorsque vous avez essayé la cigarette électronique pour la première fois ?

└┘└┘ ans

Utilisez-vous la cigarette électronique actuellement ?

☐ oui ☐ non *[Passez à la question 4.12]*

→ Si oui, à quelle fréquence utilisez-vous la cigarette électronique ?

☐ Tous les jours
☐ Moins d'une fois par jour, mais au moins une fois par semaine
☐ Moins d'une fois par semaine, mais au moins une fois par mois
☐ Moins d'une fois par mois

→ Quel est le taux moyen de nicotine dans votre liquide de cigarette électronique ?

☐ 0 mg/ml
☐ 6 mg/ml
☐ 11 ou 12 mg/ml
☐ 16 ou 18 mg/ml
☐ 19,9 mg/ml
☐ Autre, précisez : ..... mg/ml

Les questions suivantes portent sur vos habitudes vis-à-vis du cannabis et d'autres substances.

4.12. Avez-vous consommé du cannabis au cours des derniers 12 mois ?

☐ oui ☐ non *[Passez à la question 4.19]*

→ À quelle fréquence consommez-vous du cannabis ?

☐ Plusieurs fois par jour
☐ 1 à 6 fois par semaine
☐ 1 à 3 fois par mois
☐ Moins d'une fois par mois

4.13. Avez-vous déjà fumé du cannabis avant midi ?

☐ oui ☐ non

4.14. Avez-vous déjà fumé du cannabis lorsque vous étiez seul ?

☐ oui ☐ non

4.15. **Avez-vous déjà eu des problèmes de mémoire quand vous fumiez du cannabis ?**

☐ oui ☐ non

4.16. **Des amis ou des membres de votre famille vous ont-ils déjà dit que vous devriez réduire votre consommation de cannabis ?**

☐ oui ☐ non

4.17. **Avez-vous déjà essayé de réduire ou d'arrêter votre consommation de cannabis sans y parvenir ?**

☐ oui ☐ non

4.18. **Avez-vous déjà eu des problèmes à cause de votre consommation de cannabis (dispute, bagarre, accident) ?**

☐ oui ☐ non

4.19. **Vous est-t-il arrivé de prendre d'autres substances dans le but de planer, de vous sentir mieux ou de vous « défoncer » au cours des derniers 12 mois ?**

☐ oui ☐ non *[Passez au questionnaire suivant, page 21]*

→ **Si oui, lesquelles ?** *plusieurs réponses possibles*

☐ Cocaïne (chlorhydrate/base)

À quelle fréquence :
- ☐ Plusieurs fois par jour
- ☐ 1 à 6 fois par semaine
- ☐ 1 à 3 fois par mois
- ☐ Moins d'une fois par mois

Pensez à la dernière fois que vous avez consommé, où étiez-vous ?
- ☐ Chez moi
- ☐ Chez quelqu'un
- ☐ Dans la rue, dans un parc, ou dans un espace ouvert
- ☐ Dans un bar ou un pub
- ☐ Dans une boîte de nuit
- ☐ Dans un restaurant
- ☐ Autres endroits

☐ Amphétamines/Ecstasy/MDMA/Methamphétamines

À quelle fréquence :
- ☐ Plusieurs fois par jour
- ☐ 1 à 6 fois par semaine
- ☐ 1 à 3 fois par mois
- ☐ Moins d'une fois par mois

Pensez à la dernière fois que vous avez consommé, où étiez-vous ?
- ☐ Chez moi
- ☐ Chez quelqu'un
- ☐ Dans la rue, dans un parc, ou dans un espace ouvert
- ☐ Dans un bar ou un pub
- ☐ Dans une boîte de nuit
- ☐ Dans un restaurant
- ☐ Autres endroits

☐ Opiaces (Mésusage de médicaments opioïdes/héroïne)

À quelle fréquence :
- ☐ Plusieurs fois par jour
- ☐ 1 à 6 fois par semaine
- ☐ 1 à 3 fois par mois
- ☐ Moins d'une fois par mois

Pensez à la dernière fois que vous avez consommé, où étiez-vous ?
- ☐ Chez moi
- ☐ Chez quelqu'un
- ☐ Dans la rue, dans un parc, ou dans un espace ouvert
- ☐ Dans un bar ou un pub
- ☐ Dans une boîte de nuit
- ☐ Dans un restaurant
- ☐ Autres endroits

☐ Cathinones de synthèse

À quelle fréquence :
- ☐ Plusieurs fois par jour
- ☐ 1 à 6 fois par semaine
- ☐ 1 à 3 fois par mois
- ☐ Moins d'une fois par mois

Pensez à la dernière fois que vous avez consommé, où étiez-vous ?
- ☐ Chez moi
- ☐ Chez quelqu'un
- ☐ Dans la rue, dans un parc, ou dans un espace ouvert
- ☐ Dans un bar ou un pub
- ☐ Dans une boîte de nuit
- ☐ Dans un restaurant
- ☐ Autres endroits

☐ GHB/GBL

À quelle fréquence :
- ☐ Plusieurs fois par jour
- ☐ 1 à 6 fois par semaine
- ☐ 1 à 3 fois par mois
- ☐ Moins d'une fois par mois

Pensez à la dernière fois que vous avez consommé, où étiez-vous ?
- ☐ Chez moi
- ☐ Chez quelqu'un
- ☐ Dans la rue, dans un parc, ou dans un espace ouvert
- ☐ Dans un bar ou un pub
- ☐ Dans une boîte de nuit
- ☐ Dans un restaurant
- ☐ Autres endroits

☐ Cannabinoïdes de synthèse (Spice…)

À quelle fréquence :
- ☐ Plusieurs fois par jour
- ☐ 1 à 6 fois par semaine
- ☐ 1 à 3 fois par mois
- ☐ Moins d'une fois par mois

Pensez à la dernière fois que vous avez consommé, où étiez-vous ?
- ☐ Chez moi
- ☐ Chez quelqu'un
- ☐ Dans la rue, dans un parc, ou dans un espace ouvert
- ☐ Dans un bar ou un pub
- ☐ Dans une boîte de nuit
- ☐ Dans un restaurant
- ☐ Autres endroits

Veuillez répondre à chacune des questions en cochant l'énoncé correspondant le mieux à votre situation.

Au cours des **deux dernières semaines**, à quelle fréquence avez-vous été perturbé par les problèmes suivants ?

Répondez à toutes les questions s'il vous plaît.

		Jamais	Plusieurs jours	Plus de la moitié du temps	Presque tous les jours
5.1.	**Peu d'intérêt ou de plaisir à faire les choses**	☐	☐	☐	☐
5.2.	**Vous sentir triste, déprimé ou sans espoir**	☐	☐	☐	☐
5.3.	**Difficultés à vous endormir, à rester endormi ou à trop dormir**	☐	☐	☐	☐
5.4.	**Vous sentir fatigué ou avoir peu d'énergie**	☐	☐	☐	☐
5.5.	**Peu d'appétit ou trop d'appétit**	☐	☐	☐	☐
5.6.	**Mauvaise perception de vous-même, vous pensez que vous êtes un raté ou que vous n'avez pas répondu à vos propres attentes ou à celles de votre famille**	☐	☐	☐	☐
5.7.	**Difficultés à vous concentrer sur des choses telles que lire le journal ou regarder la télévision**	☐	☐	☐	☐
5.8.	**Vous bougez ou vous parlez si lentement que les autres personnes ont pu le remarquer. Ou, au contraire, vous êtes si agité que vous bougez beaucoup plus que d'habitude**	☐	☐	☐	☐
5.9.	**Vous avez pensé qu'il serait mieux que vous soyez mort, ou à vous faire du mal d'une façon ou d'une autre**	☐	☐	☐	☐

5.10. **A quel point ce(s) problème(s) a-t-il (ont-ils) rendu votre travail, vos tâches à la maison ou votre capacité à vous entendre avec les autres difficile(s) ?**

☐ Pas du tout difficile(s)
☐ Plutôt difficile(s)
☐ Très difficile(s)
☐ Extrêmement difficile(s)

Merci de votre participation,

veuillez remettre ce questionnaire à votre médecin ou au secrétariat de son service.

Annex VI: Home page www.qualiv.fr

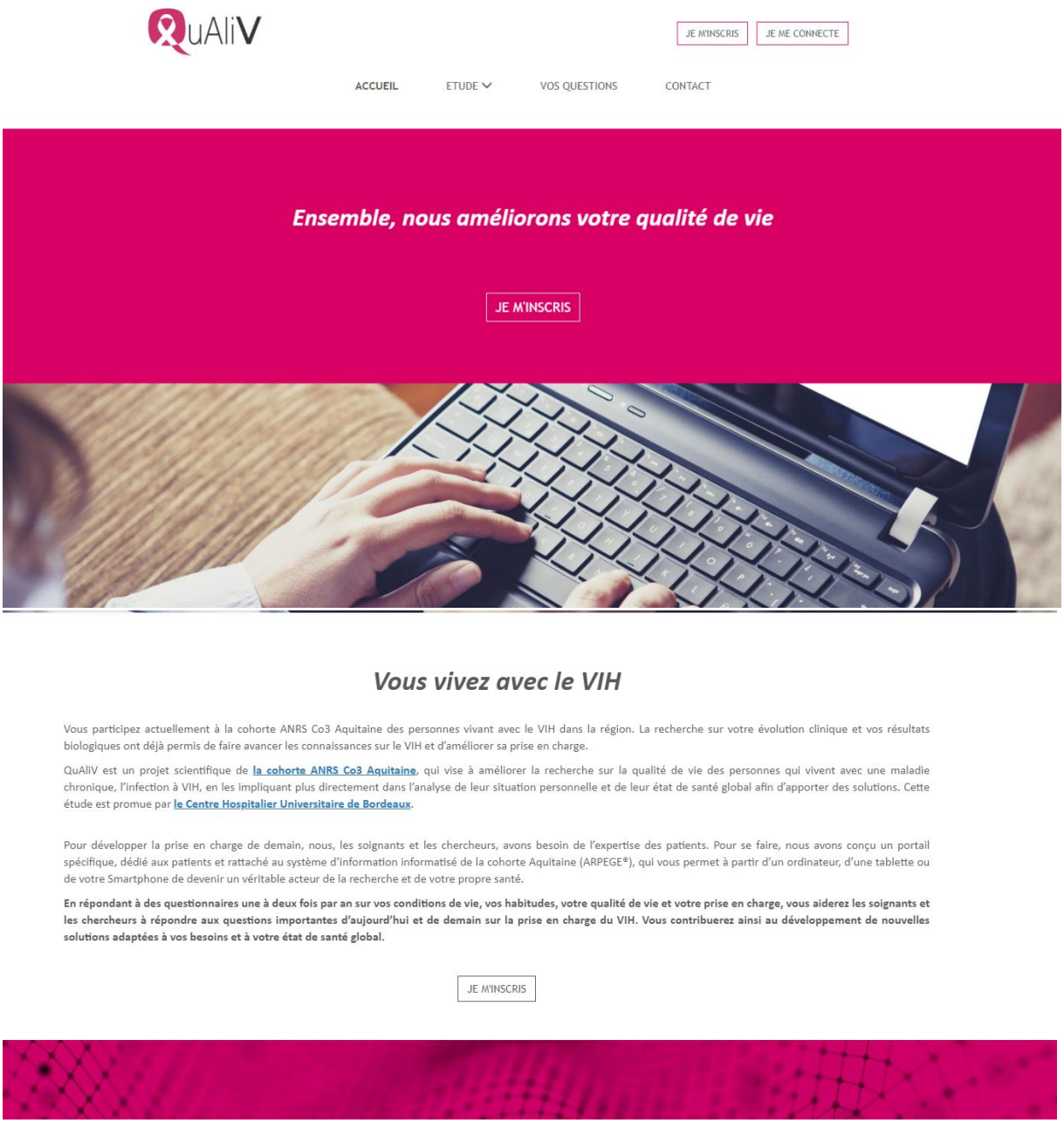


FIGURE 9 : HOME PAGE

Annex VII: Account creation

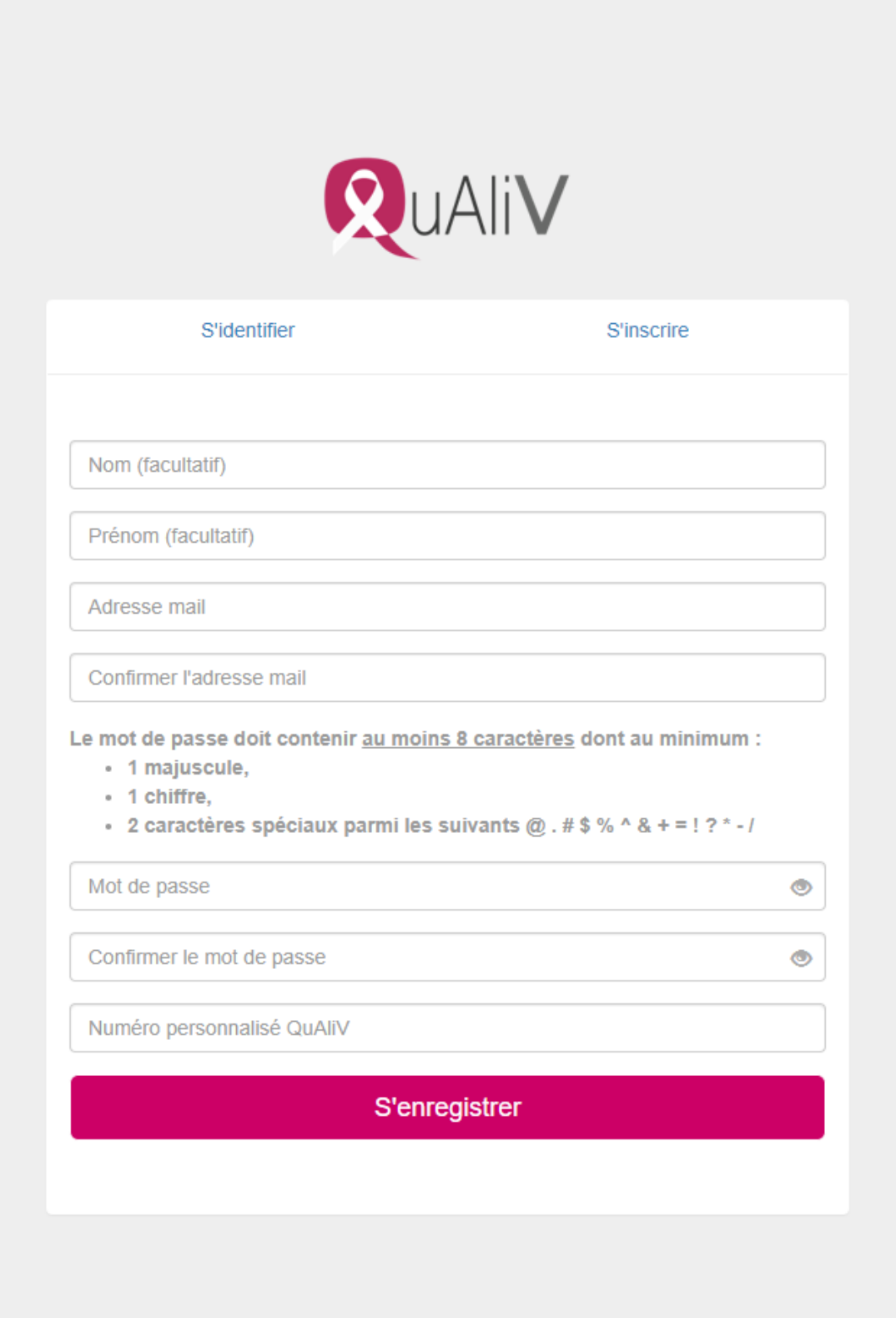


FIGURE 10: ACCOUNT CREATION PAGE

Annex VIII : Inclusion procedure from the perspective of the investigator and CRA.

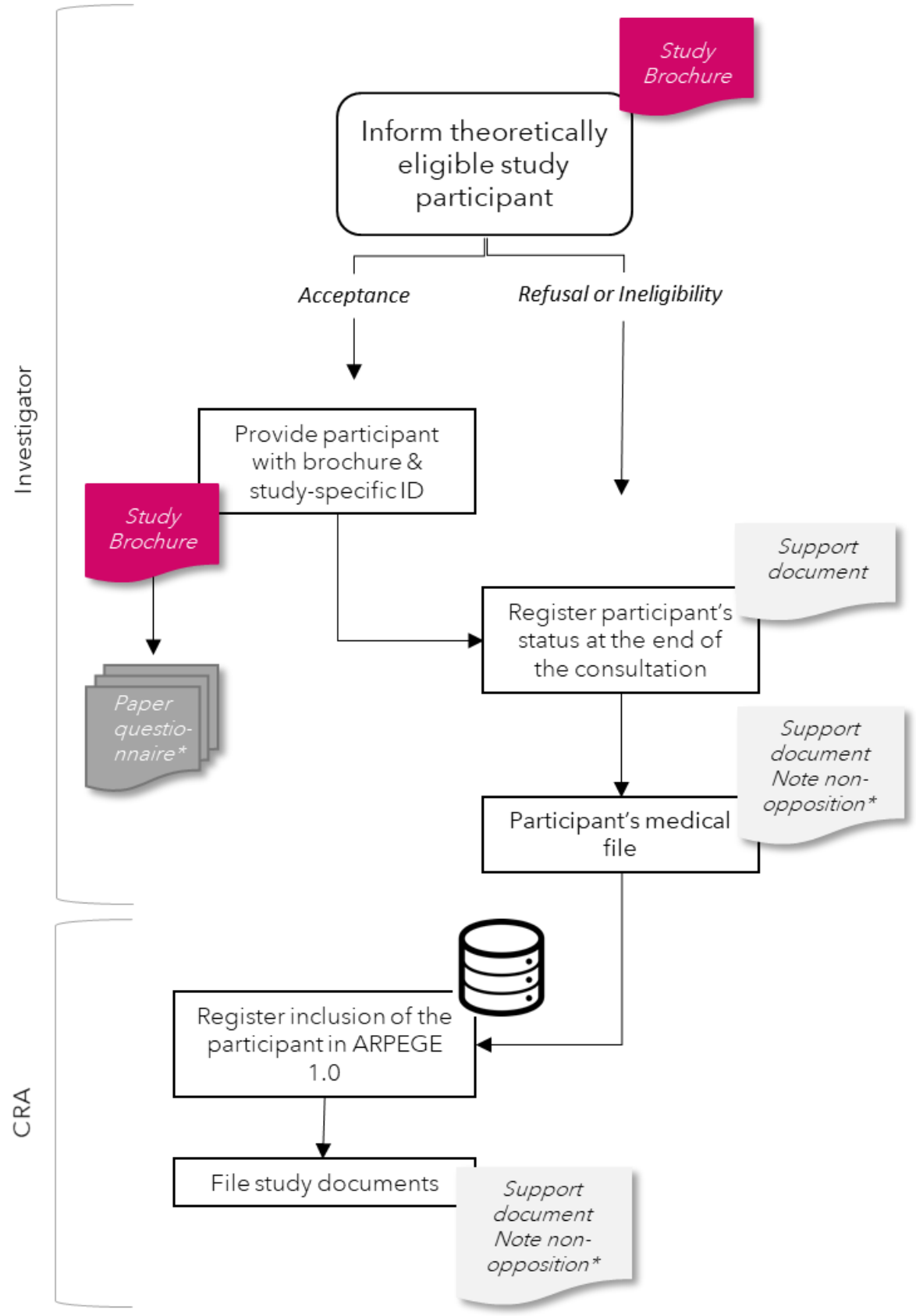


FIGURE 11: INCLUSION PROCEDURE FROM THE PERSPECTIVE OF THE INVESTIGATOR AND CRAS

Résumé

L'infection par le VIH est devenue une maladie chronique en France. Néanmoins, le VIH et l'inflammation associée, les effets de l'exposition aux antirétroviraux, la prévalence élevée de facteurs de risque modifiables pour les maladies liées à l'âge, les effets d'autres co-infections virales couplés à la vulnérabilité sociale et économique font de la qualité de vie des personnes vivant avec le VIH (PVVIH) une préoccupation constante. Les recommandations de prise en charge incitent à prendre en compte la santé des PVVIH telle que définie par l'Organisation Mondiale de la Santé. Nous avons cherché à relever ce défi en concevant un module relié au système d'information de la Cohorte ANRS CO3 Aquitaine qui facilite le recueil de données rapportées par les patients (y compris la qualité de vie) par le biais d'instruments validés. Le contenu (composé de questionnaires courts et validés) du système est basé sur les recommandations thérapeutiques. Les propriétés psychométriques, la méthode et le mode d'administration ainsi que la longueur des questionnaires ont été évalués et des instruments papier ont été adaptés au format numérique selon les recommandations de l'International Society for Pharmacoeconomics and Outcomes Research. Les tests d'utilisabilité du nouveau module du système d'information se sont déroulés en deux cycles (1er auprès des experts et 2ème auprès des PVVIH). Nous avons demandé aux participants d'accomplir une série de tâches en utilisant la méthode « penser à voix haute » et de répondre à l'échelle de « System Usability Scale » (SUS). Nous avons calculé un score synthétique et défini a priori le « succès » comme un score d'utilisabilité de 70. Au premier cycle, les experts ont rapporté des scores SUS moyens de 65 ± 18,87 et les patients, au deuxième cycle, des scores SUS moyens de 85 ± 5,4 (p=0,032). A ce jour, le recueil (électronique et papier) de données rapportées par les patients, y compris la qualité de vie liée à la santé, est en cours dans cinq hôpitaux de la région Nouvelle Aquitaine. Parmi ceux qui ont été invités à participer (juillet 2018-mai 2019), 90,5% (1 521/1 681) ont accepté, 7,1 % (119/1 681) ont refusé et 2,4 % (41/1 681) étaient non- éligibles. Parmi ceux qui ont accepté, 82% (1246/1 521) ont été considérés comme ayant satisfait aux exigences de base du nouveau système d'information tandis que 18 % (275/1 521) n'avaient pas d'adresse courriel personnelle. Les propriétés métriques de l'instrument de mesure choisi pour évaluer la qualité de vie (liée à la santé) dans notre population ont été ensuite évaluées sur un échantillon de 586 PVVIH, âgées de 56 ans en moyenne. 73 % étaient des hommes, 85 % étaient d'origine française, 99% étaient sous antirétroviraux et 93 % avaient une charge virale indétectable. La version française du WHOQOL-HIV BREF a des propriétés de mesure acceptables et sa conceptualisation large de la qualité de vie (au-delà de la santé physique et mentale) peut s'avérer particulièrement utile dans notre population. Sur une échelle de 4 à 20, le domaine des croyances personnelles avait le score moyen le plus élevé (15,04 ± 3,35) et le domaine de la santé psychologique le plus faible (13,70 ± 2,78). Les aspects (score de 1 à 5) les plus altérés étaient les relations personnelles (2,7 ± 1,25) et les ressources financières (2,9 ± 1,15). Les femmes ont obtenu des scores nettement inférieurs à ceux des hommes pour 12 sur 29 aspects, y compris les cinq aspects spécifiques au VIH. Les personnes nées en Afrique du Nord ou en Afrique subsaharienne ont des score plus faibles dans le domaine « environnement de vie » que celles nées en France (13,19 ± 2,10 contre 14,52 ± 2,56, p<0,001). Cette nouvelle démarche a été la première étape dans l'établissement d'un nouveau rapport avec les personnes prises en charge dans la région. Elle a permis de mettre en lumière des domaines qui, selon nous, doivent être particulièrement ciblés afin de développer avec succès de nouveaux modèles de soins et de services sociaux qui tiennent compte des besoins globaux des PVVIH et y répondent efficacement.

Mots clés : qualité de vie liée à la santé, données rapportées par les patients, maladies chroniques, e-santé, VIH

Abstract

HIV has become a chronic disease in France. Nevertheless, HIV and associated inflammation, the effects of antiretroviral exposure, the high prevalence of modifiable risk factors for age-related diseases (e.g. smoking) and the effects of other viral co-infections together with social and economic vulnerability make the quality of life of people living with HIV (PLWH) an ongoing concern. French clinical guidelines have urged providers to address PLWH's health as defined by the World Health Organisation. To take on this challenge, we designed an electronic module for the collection of patient-reported outcome linked the ANRS Aquitaine cohort's data capture and visualisation system. The proposed solution relies on validated questionnaires and its content is based on current clinical guidelines on HIV management. The questionnaires' psychometric properties, administration method/mode, and length were evaluated and paper-based instruments adapted following the International Society for Pharmacoeconomics and Outcomes Research's guidance. Two rounds of usability evaluations were conducted first in research staff and the PLWH. We asked participants to complete a set of tasks using the 'think aloud' method and respond to the System Usability Scale (SUS). Input from experts/investigators and subsequently patients was used to improve features of the system. We calculated a summary score and defined "success" a priori as a usability score of 70. Experts reported average SUS scores of 65 ± 18.87 and patients reported average SUS scores of 85 ± 5.4 (p=0.032). To date, the collection of (electronic and paper) patient-reported outcomes, including health-related quality of life, is underway in five hospitals. Of those invited to participate (July 2018-May 2019), 90.5% (1,521/1,681) accepted, 7.1% (119/1,681) refused and 2.4% (41/1,681) were not eligible. Of those who accepted, 82% (1,246/1,521) were considered to have met the basic requirements of the newly designed solution whereas 18% (275/1,521) did not have a personal email address and/or a reliable Internet connection and were provided an identical paper questionnaire. We verified the psychometric properties of the WHOQOL-HIV BREF instrument, chosen to assess (health-related) quality of life in our population in a sample of 586 PLWH (aged 56 on average, 73% were male, 85% were of French origin, 99% were treated and 93% had an undetectable viral load). The French version of the WHOQOL-HIV BREF has acceptable measurement properties and its broad conceptualization of quality of life, going beyond physical and mental health, may be particularly useful in our population. On a scale of 4 (worst) to 20 (best), the personal belief domain had the highest average score (15.04 ± 3.35) and the lowest psychological health domain (13.70 ± 2.78). The most impaired facets (score of 1-5) were personal relationships (2.7 ± 1.25) and financial resources (2.9 ± 1.15). Women scored significantly lower than men on 12 of 29 facets, including the five HIV-specific facets. People born in North Africa or sub-Saharan Africa have lower scores in the environmental health domain than those born in France (13.19 ± 2.10 versus 14.52 ± 2.56, p<0.001). This work has been the first step in fostering a new relationship with those in care in the region. It has resulted in highlighting a number of areas that we feel need to be addressed in order to successfully develop new value-based models of care and social services which take into consideration and efficiently respond to PLWH's global needs.

Key words: health-related quality of life, patient-reported outcomes, chronic diseases, e-health, HIV