

Integration and generalization of "Universal Test and Treat" strategies for HIV in sub-Saharan Africa : The ANRS 12249 TasP Trial and beyond

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université de BORDEAUX

THÈSE PRÉSENTÉE

POUR OBTENIR LE GRADE DE

DOCTEUR DE L'UNIVERSITÉ DE BORDEAUX

ÉCOLE DOCTORALE : Sociétés, Politique et Santé publique

SPÉCIALITÉ : Santé Publique

OPTION: Epidémiologie

Par Delphine PERRIAT

Intégration et généralisation des stratégies du type "Dépistage et traitement universels du VIH" en Afrique sub-saharienne Exemple de l'essai ANRS 12249 TasP

Integration and generalization of "Universal Test and Treat" strategies for HIV in sub-Saharan Africa The ANRS 12249 TasP Trial and beyond

Sous la direction de : Joanna ORNE-GLIEMANN et François DABIS

Soutenue le 12 décembre 2017

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ADMINISTRATIVE INFORMATION

The present PhD was realized within the "Infectious diseases in lower-income countries" (IDLIC) research team, in the Bordeaux Population Health research centre INSERM U1219, University of Bordeaux, located 146 rue Léo Saignat, 33076 BORDEAUX

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EPIGRAPH

“Toutes les généralisations sont fausses, y compris celle-ci”

“All generalizations are dangerous, even this one.”

- Alexandre Dumas

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Figure 1: The ANRS 12249 TasP trial field staff

SYNTHESE DE LA THESE (FRANÇAIS)

Introduction

En 2016, il était estimé que 36,7 millions de personnes vivaient avec le VIH dans le monde, qu'il y avait eu 2,1 millions de nouvelles infections et 1,1 million de décès. L'Afrique subsaharienne restait de loin la région la plus touchée, regroupant près de 70% des personnes infectées, 66% des nouvelles infections et 74% des décès liés au sida cette année-là [1].

La récente vague d'optimisme pour le contrôle de l'épidémie de VIH repose en grande partie sur les traitements antirétroviraux (TARVs) [2]. Il a été démontré que l'instauration d'un TARV le plus tôt possible après le diagnostic du VIH (quel que soit le stade de la maladie) non seulement procurait de forts bénéfices cliniques individuels [3, 4], mais avait aussi le potentiel d'éliminer la transmission du VIH par voie sexuelle. Les bénéfices préventifs du TARV sur la transmission de l'infection ont été mis en évidence dans des études observationnelles et écologiques [5, 6] ainsi que dans l'essai randomisé contrôlé HIV Prevention Trial Network (HPTN) 052 [7].

Sur la base de ces résultats encourageants, l'Organisation mondiale de la santé (OMS) a recommandé en 2015 que les TARVs soient offerts à toute personne diagnostiquée séropositive, indépendamment de son nombre de cellules CD4 et de son stade clinique [8]. Le programme commun des Nations Unies sur le VIH / SIDA. (ONUSIDA) a proposé les objectifs 90-90-90 pour mettre fin à l'épidémie de sida d'ici 2020 (90% des personnes infectées par le VIH connaissent leur statut VIH, 90% de celles qui connaissent leur statut VIH positif prennent un TARV, et 90% de ceux sous TARV ont une charge virale indétectable) [9].

Les modèles mathématiques prédisent que l'initiation immédiate d'un TARV après un diagnostic VIH positif pourrait réduire l'incidence du VIH de façon spectaculaire dans le cadre d'une stratégie de dépistage et de traitement universel du VIH (Tester et Traiter Universellement (TTU)) qui inclut une offre régulière de dépistage et conseil du VIH à toute une population et une offre de TARV à tous ceux diagnostiqués VIH+ [10-12]. Dans un contexte où les financements alloués à la riposte au VIH sont stables, il est essentiel d'obtenir des preuves de l'impact à long terme des stratégies TTU et d'ainsi mesurer leur potentiel en tant que mesures de santé publique [13, 14]. Pour répondre à ce besoin, plusieurs projets de recherche, ont évalué ou évaluent actuellement l'efficacité des stratégies TTU contre l'épidémie de VIH. Ainsi, cinq essais randomisés contrôlés sont en cours en Afrique sub-saharienne : BCPP / YaTsie au Botswana [15], MaxART au Swaziland [16], HPTN 071 (PopART) en Afrique du Sud et en Zambie [17], SEARCH en Ouganda et Kenya[18] et ANRS 12249 TasP (TasP) en Afrique du Sud [19].

Justification et objectifs de thèse

L'optimisation de l'impact d'une stratégie TTU requière l'atteinte de taux d'utilisation des services VIH qui sont sans précédent. Dans un tel contexte, des questions de recherche urgentes se posent sur la faisabilité, l'acceptabilité et le ratio coût-efficacité des stratégies du type TTU [2]. Ces éléments de preuve seront essentiels pour guider les politiques et les pratiques futures dans l'optimisation des systèmes de santé actuels vers le développement d'une offre de dépistage et traitement universels. Mon doctorat propose de répondre à certaines de ces

questions. J'ai concentré mon travail sur trois lacunes de la littérature scientifique, en prenant comme exemple l'essai TasP. Tout d'abord, comme il n'y a pas de recommandation claire, pas de «package d'interventions idéal» à mettre en place pour garantir le succès de la stratégie TTU, nous ne savons pas comment cette stratégie a été comprise, définie et mise en œuvre dans divers contextes. Nous ne savons pas non plus comment les travailleurs de santé exposés au TTU comprennent et s'approprient cette stratégie. Enfin, nous ne savons pas comment les personnes exposées au TTU se comportent lorsque ces interventions novatrices sont proposées dans leur routine de soins.

L'objectif de ma thèse était d'explorer les conditions de mise en œuvre d'une stratégie TTU à large échelle en Afrique sub-saharienne, en prenant l'exemple de l'essai TasP. Cet objectif général fut divisé en trois objectifs spécifiques : 1. Caractériser et comparer les approches TTU des 5 essais randomisés populationnels en Afrique sub-saharienne, 2. Décrire les expériences et les perceptions des travailleurs de santé sur la faisabilité et l'acceptabilité de la stratégie TTU au sein de l'essai TasP, 3. Analyser les trajectoires de soins des personnes vivant avec le VIH dans le cadre d'une offre de soins de TTU au sein de l'essai TasP.

Cadre de travail

Mon travail de thèse a été intégré dans le programme de recherche de l'équipe pluridisciplinaire de l'essai TasP, née d'un partenariat franco-sud-africain privilégié entre l'équipe de recherche française "Maladies infectieuses dans les pays à faible revenu (IDLIC)", dirigée par Xavier Anglaret et intégrée au centre de recherche Inserm U1219 Bordeaux Population Health ; et le centre de recherche sud-africain Africa Health Research Institute (AHRI) dirigé par Deenan Pillay depuis 2013, financé par le Wellcome Trust et affilié à l'Université du KwaZulu-Natal. Mes deux directeurs de thèse développent leurs recherches au sein de l'équipe IDLIC : Joanna Orne-Gliemann est chercheuse en santé publique, co-directrice du Master "Santé Internationale " à l'école de santé publique de Bordeaux (ISPED). Elle a co-coordonné l'essai TasP. François Dabis est professeur d'épidémiologie à l'école de santé publique de Bordeaux. Il est l'ancien directeur de l'équipe IDLIC et actuel directeur de l'Agence nationale française de recherche sur le sida et les hépatites virales (ANRS). Il était co-investigateur principal de l'essai TasP.

L'essai TasP a été mené dans le sous-district de Hlabisa au sein du district d' uMkhanyakude, dans la province du KwaZulu-Natal en Afrique du Sud. Hlabisa est une zone de 1 430 km2 avec une population d'environ 248 000 habitants [20]. La majorité de la communauté vit dans des maisons dispersées, qui ne sont pas concentrées dans des villages. C'est l'une des régions les plus défavorisées d'Afrique du Sud, avec 43% de chômage et seulement 37% de la population qui a accès à l'eau courante [20]. C'est un exemple typique d'une zone rurale qui paye un lourd tribut en vies humaines au VIH [21]. L'incidence brute du VIH a été estimée à 2,63 nouvelles infections pour 100 personnes-années (IC à 95% 2,50-2,77) chez les personnes de 15 ans et plus entre 2004 et 2011 dans la zone de surveillance démographique du centre AHRI [22]. La prévalence estimée du VIH était de 29% en 2011 parmi les 15-49 ans [23]. L'une des principales caractéristiques du système de santé local actuel est la décentralisation des soins de santé primaires [24]. Il y a 17 cliniques locales dans la zone de Hlabisa. Les infirmières sont en charge de la gestion des cliniques, y compris du programme de TARV. Un médecin de l'hôpital de Hlabisa visite chaque clinique une fois par mois. Au lancement de l'essai TasP, 37% des personnes qui vivaient avec le VIH seulement avaient accès à un TARV dans la zone de surveillance démographique du centre AHRI [22].

L'essai TasP était un essai randomisé par grappes avec deux bras de randomisation (expérimental et témoin) mis en œuvre entre mars 2012 et juin 2016 dans 22 grappes (2 x 11) pour étudier l'impact du TARV sur l'incidence du VIH [19]. L'essai comportait deux volets d'interventions de soin VIH : le premier était une offre répétée de dépistage du VIH à domicile tous les six mois, via des tests rapides et le référencement des personnes séropositives aux cliniques de l'essai – une par grappe; le deuxième portait sur les soins cliniques proposés aux personnes séropositives au sein des cliniques de l'essai. Dans le bras expérimental de l'essai, les personnes séropositives adultes recevaient un TARV dès leur visite dans une clinique de l'essai. Dans le bras témoin de l'essai, elles recevaient un TARV conformément aux directives nationales en vigueur : CD4 ≤350 cellules / mm^3, stade d'évolution de la maladie 3 ou 4 selon l'OMS ou tuberculose pharmaco-résistante jusqu'en janvier 2015 [25], puis ≤500 cellules / mm^3 jusqu'à la fin de l'essai [26].

Méthodes, résultats et discussion

En intégrant ma thèse au sein de l'essai TasP, j'ai pu utiliser des données de qualité pour étudier la mise en œuvre de la stratégie TTU: données de tous les essais TTU en Afrique sub-saharienne via une collaboration inter-essais à laquelle l'essai TasP participait, données quantitatives et qualitatives recueillies de manière transversale parmi les travailleurs de santé dans la zone de l'essai TasP ; et données longitudinales quantitatives décrivant les parcours de soins des participants à l'essai TasP.

1. Évaluation comparative de cinq essais de dépistage et de traitement universels du VIH en Afrique subsaharienne

Pour ce premier volet de la thèse dont l'objectif était de caractériser et comparer les approches TTU des 5 essais cliniques populationnels en Afrique subsaharienne, nous avons effectué une évaluation comparative de ces cinq essais en utilisant leurs protocoles d'étude et des données recueillies à leur commencement. Nous avons organisé les différences et des points communs entre essais en cinq catégories: contextes, méthodologies de recherche, interventions, thèmes étudiés et adaptations du design d'essai.

Grâce à ce premier travail, nous avons mis en évidence que tous les essais TTU étudiés étaient réalisés dans des contextes d'épidémies de VIH généralisées, et qu'ils adoptaient une stratégie de TTU adaptée à leurs divers contextes sociaux, démographiques, économiques, politiques et de système de santé. Tous ces essais partagent l'objectif commun d'évaluer l'impact d'une stratégie TTU sur l'épidémie de VIH, mais diffèrent par des aspects méthodologiques tels que le design d'étude et les critères d'éligibilité des populations d'étude. En plus de l'initiation immédiate du TARV, les essais fournissent une sélection de services de santé choisis parmi un large éventail d'interventions de prévention du VIH et de prise en charge d'autres maladies. Les cinq essais ont adopté une approche pluridisciplinaire et étudient des thèmes communs, y compris les taux d'utilisation des services de soins et les résultats cliniques individuels ainsi que les barrières et facilitateurs à l'accès aux soins.

En l'absence actuelle de recommandations précises sur la mise en place à large échelle d'une stratégie TTU dans une communauté entière, l'article, qui a été approuvé pour publication, fournit une base pour une recherche plus collaborative sur le TTU et attire l'attention sur le fait que ces essais TTU communautaires fournissent des pistes pour éclairer les politiques de santé

dans l'optimisation des systèmes de santé actuels vers le développement d'une offre de soins VIH universelle.

2. Expériences et perceptions des travailleurs de santé sur une offre de dépistage et de traitement universels du VIH en zone rurale sud-africaine

Ce second volet de la thèse avait pour objectif d'explorer les expériences et les perceptions des travailleurs de santé à propos d'une offre de services VIH dans le cadre d'une stratégie TTU afin d'améliorer la cascade de soins des personnes vivant avec le VIH en zone rurale sud-africaine. Nous avons mené une étude quantitative et qualitative auprès des travailleurs de santé de l'essai TasP et des cliniques gouvernementales locales du sous-district de Hlabisa d'avril à juillet 2016. Nous avons utilisé des questionnaires auto-administrés (n = 90 dans l'essai TasP, n = 56 dans les cliniques gouvernementales), des entretiens semi-structurés (n = 13 dans l'essai TasP, n = 5 dans les cliniques gouvernementales) et trois groupes de discussion (n = 6-10 participants de l'essai TasP par groupe). Des statistiques descriptives ont été utilisées pour les données quantitatives et les données qualitatives ont été analysées par thème.

Dans un premier temps, nous nous sommes intéressés aux opinions des travailleurs de santé concernant la faisabilité et l'acceptabilité de services VIH à domicile, y compris le conseil et dépistage rapide du VIH ainsi que les actions de soutien pour encourager l'entrée et le maintien dans les soins VIH. Nous avons ainsi mis en évidence que plus de 90% des travailleurs de santé évaluaient le dépistage à domicile et le soutien pour l'entrée dans les soins, comme faisable et acceptable par la population avec laquelle ils travaillent. Nombre d'entre eux ont souligné que les visites à domicile pouvaient faciliter l'accès en clinique aux personnes qui étaient passées entre les mailles du système de soins. Ils ont remarqué le potentiel de la relation patient-professionnel de santé, initiée en dehors du cadre de la clinique, à encourager les patients à rester dans les soins de manière durable. Les agents de santé ont toutefois exprimé des inquiétudes quant à la capacité des services à domicile à répondre aux besoins de tous les membres de la communauté, notamment ceux qui travaillent et ne sont donc pas présents à leur domicile lors des visites ou ceux qui craignent la stigmatisation liée au VIH. Dans l'ensemble, les travailleurs de santé ont encouragé les décideurs de santé publique à faire des services à domicile une part intégrante du système de santé local, et à intégrer les soins VIH à une offre de santé plus globale

Parce que les services à domicile permettent l'identification des personnes au début de leur infection et encouragent leur confiance dans l'utilisation des services de soins, les travailleurs de santé les ont évalués comme des éléments utiles dans le panel des interventions de TTU, visant à atteindre les objectifs 90-90-90 de l'ONUSIDA, notamment dans la région rurale d'Afrique du Sud dans laquelle ils travaillent.

Dans un second temps, nous avons cherché à décrire les expériences et les perceptions des travailleurs de santé concernant la mise en œuvre du TARV universel. Nous avons observé que tous les professionnels de santé avaient des expériences très positives relatives au TARV proposé tôt au cours de l'infection par le VIH. Bien qu'ils aient déclaré que la plupart de leurs patients étaient enthousiastes à l'idée d'initier un TARV avant d'être symptomatique, plusieurs d'entre eux ont souligné que l'absence de symptôme restait une barrière notable à l'initiation précoce et à l'observance à long-terme du TARV. Ils ont mis en avant l'importance de dédier suffisamment de temps au conseil de leurs patients pour les accompagner dans l'acceptation du

TARV universel. Les professionnels de santé ont prévu également des défis logistiques liés à la mise en place du TARV universel à large échelle. Ils étaient particulièrement préoccupés par l'augmentation de leur charge de travail et la possibilité d'une pénurie de TARV. Par ailleurs, ils ont recommandé l'importance d'accompagner la mise en place du TARV universel par un renforcement du modèle de soins existant, par exemple grâce à une intégration des services VIH à une offre de soin plus globale, notamment délivrés directement dans les communautés.

Pour conclure, la mise en place du TARV universel à large échelle apparait faisable et acceptable aux professionnels de santé interrogés dans cette zone rurale sud-africaine. Cependant, ils s'accordent à dire qu'atteindre une couverture universelle en TARV, et plus généralement atteindre les objectifs 90-90-90 de l'ONUSIDA, nécessitera une nette adaptation du modèle de soins actuels.

3. Trajectoires de soins VIH du dépistage à la suppression virale dans le contexte d'une offre de dépistage et traitement universels en Afrique du Sud rurale

Ce troisième et dernier volet de ma thèse avait pour objectif de décrire la succession des événements de soins VIH de chaque individu, du dépistage à la suppression de la charge virale, en identifiant des groupes d'individus ayant des trajectoires de soins similaires et en mettant en évidence les facteurs associés à chaque groupe. Pour cela nous avons utilisé les données longitudinales prospectives de l'essai TasP. Nous avons tout d'abord attribué un statut journalier de prise en charge à tous les participants de l'essai TasP âgés de plus de 16 ans, identifiés VIH +, non pris en charge dans les soins au début de l'essai et suivis pendant plus de 18 mois. Les quatre statuts journaliers possibles étaient les suivants: non pris en charge, pris en charge mais pas sous TARV, sous TARV mais dont la charge virale n'est pas indétectable, charge virale indétectable. Nous avons ensuite utilisé une technique d'analyse de séquences pour identifier des groupes homogènes de trajectoires de soins. Puis nous avons caractérisé le profil de chaque groupe de trajectoires (e.g. caractéristiques individuelles des participants des groupes) avec une régression logistique multinomiale.

Dans cette analyse, nous avons inclus 1 816 participants VIH + de l'essai TasP. L'âge médian était de 34 ans [intervalle interquartile: 27-45], 74% étaient des femmes. Nous avons identifié quatre groupes de trajectoires de soins (Figure): (i) les participants qui ne recevaient pas de soins (55%), (ii) les participants qui ont accédé brièvement aux soins, visitant une clinique une fois mais abandonnant les soins juste après [5.2-13]) (12%), (iii) les participants qui ont pris beaucoup de temps à chaque étape du continuum des soins (temps médian entre le dépistage et le début du TARV: 8,0 mois [6,4-9,7]) (12%) (iv) les participants qui ont rapidement progressé vers les soins (temps médian entre le dépistage et le début du TARV: 1,2 mois [0,6-2,7]) (21%). Les participants qui vivaient à plus d'un kilomètre d'une clinique, qui recevaient un diagnostic précoce et qui recevaient un TARV selon les recommandations nationales (vs TARV universel), étaient plus susceptibles de présenter des trajectoires incomplètes et lentes.

Pour conclure, les trajectoires de soins des participants à l'essai TasP se sont révélées être très hétérogènes. Afin de maximiser l'impact des stratégies de dépistage et traitement universel, des soins personnalisés et une offre de soutien à l'accès aux soins devraient être mis en œuvre, en particulier pour la période cruciale située entre le dépistage et l'initiation du TARV, qui rassemble le plus de sorties de soins dans cette zone rurale sud-africaine.

Conclusions et perspectives

Les résultats rapportés dans cette thèse documentent la mise en œuvre d'une stratégie TTU à large échelle. Ils participent à fournir aux décideurs de santé publique des preuves pertinentes permettant de guider l'utilisation des ressources disponibles pour assurer un impact maximal d'une stratégie TTU sur la santé des populations en Afrique sub-Saharienne.
La première observation générale de cette thèse a été la mise en évidence de la diversité des interventions de prise en charge du VIH au sein d'une stratégie TTU. Les interventions les plus prometteuses dans la lutte contre l'épidémie ont été testées au sein des essais communautaires TTU qui ont été conduit en Afrique subsaharienne. Outre l'évaluation de l'impact de ces interventions sur l'incidence du VIH, ces essais sont une mine d'informations concernant leur faisabilité, leur acceptabilité et leur ratio coût-efficacité. L'interdisciplinarité de la recherche apporte de précieuses perspectives aux décideurs et planificateurs qui font face à une épidémie de VIH en constante évolution [27].

Deuxièmement, notre recherche a donné la parole à ceux qui sont au cœur des services de soins : les professionnels de santé. Elle a souligné le potentiel d'une relation de confiance établie entre un professionnel et son patient dans un environnement propice comme le domicile du patient, pour encourager l'accès aux soins. Ces résultats appellent à une recherche accrue pour évaluer l'impact de la délégation des tâches et de la prestation de soins en dehors des cliniques dans la réponse aux besoins de santé des populations, à l'heure où la dernière décennie a mis en évidence des lacunes importantes dans la disponibilité, l'accessibilité et la qualité du personnel de santé [28, 29].

Le dernier résultat important de notre recherche concerne l'utilisation des services VIH par des personnes qui bénéficient d'une offre de type TTU. Nous avons mis en évidence une hétérogénéité des comportements individuels, soulignant le nombre importants de personnes qui sortent des soins [30]. Alors que nombre de pays d'Afrique sub-Saharienne adoptent la recommandation du TARV universel dans leur politique nationale [31], des questions de recherche émergent pour encourager l'accès aux soins, notamment via l'individualisation de l'offre de santé [32] et l'utilisation de systèmes d'information pour le suivi des individus [33].

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LIST OF ABBREVIATIONS

ACCDB	Clinical database of the Africa health research institute
AHRI	Africa health research institute
AIDS	Acquired immune deficiency syndrome
ANRS	French National Agency for AIDS and Viral Hepatitis Research
ART	Antiretroviral treatment
ARV	Antiretroviral drugs
BREC	Biomedical Research Ethical Council
CCG	Community caregiver
CI	Confidence Interval
EHESP	Ecole des hautes études en santé publique – School of Public Health
FGD	Focus Group Discussion
HAART	Highly-active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCW	Health care workers
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trial Network
IDLIC	Infectious diseases in lower income countries research team
IeDEA	International epidemiological database to evaluate AIDS
IMAGE	Intervention with microfinance for AIDS and gender equity project
ISPED	Bordeaux school of public health (Institut de Santé Publique, d'épidémiologie et de développement)
MEREVA	French clinical trial unit for lower-income countries
NGO	Non-governmental organization
NHLS	National health laboratory services database
NIMART	Nurse-initiated management of antiretroviral therapy
OST	Opioid substitution therapy
PEP	Post-exposure prophylaxis
PEPFAR	US President's Emergency Plan for AIDS Relief
PIPSA	Population Intervention Platform Study Area
PMTCT	Prevention of mother-to-child transmission of HIV
PreP	Pre-exposure prophylaxis
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
RR	Relative risk
SSI	Semi-structured interview
STI	Sexually transmitted infection
TasP	Treatment-as-prevention ANRS 12249 trial
TB	Tuberculosis mycobacterium
UNAIDS	Joint United Nations programme on HIV/AIDS
UTT	Universal test and treat
UT^3C	Universal Test and Treat Trials Consortium
VMMC	Voluntary male medical circumcision
WHO	World Health Organization

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Perriat D, Plazy M, Gumede D, Boyer S, Pillay D, Dabis F, Seeley J, Orne-Gliemann J, for the ANRS 12249 TasP Study Group. Implementing universal HIV treatment in a high HIV prevalence and rural South African setting - Field experiences and recommendations of health care providers. PloS one. 2017;12(11):e0186883.

Submitted/under revision manuscript

Perriat D, Plazy M, Gumede D, Boyer S, Pillay D, Dabis F, Seeley J, Orne-Gliemann J, for the ANRS 12249 TasP Study Group. "If you are here at the clinic, you do not know how many people need help in the community.": perspectives of home-based HIV services from health care workers in rural KwaZulu-Natal, South Africa, in the era of Universal Test-and-Treat. (PloS one)

Manuscript in preparation

Perriat D, Diallo H, Dabis F, Pillay D, Orne-Gliemann J, Larmarange J, for the ANRS 12249 TasP Study Group. From Home-based HIV testing to viral suppression: HIV care trajectories in the context of Universal-Test-and-Treat in rural South Africa. (Targeted journal: AIDS)

Oral communications

Perriat D, Diallo H, Dabis F, Pillay D, Orne-Gliemann J, Larmarange J, for the ANRS 12249 TasP Study Group. From Home-based HIV testing to viral suppression: HIV care trajectories in the context of Universal-Test-and-Treat in rural South Africa, Life History Research Society Conference 2018, May 30th – June 1st 2018, Paris, France (Abstract ID number 0C4C; http://lhrs2018paris.com/programme/preliminary-programme/). Oral communication to be done on the 31st of May 2018.

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GENERAL INTRODUCTION

By the end of 2015, an estimated 36.7 million persons were living with human immunodeficiency virus (HIV) in the world, with an estimated 2.1 million new infections and 1.1 million deaths. Sub-Saharan Africa remained by far the hardest-hit region, accounting for 70% of the people infected, 66 % of the new infections and 74% of the acquired immune deficiency syndrome (AIDS) related deaths that year [34].

Recent optimism to curb the HIV epidemic has rested in large parts on antiretroviral treatments (ART) [2]. First, initiating ART as soon as possible after HIV diagnosis (regardless of disease stage) has been shown to yield strong clinical benefits to the individual [3, 4]. Then, initiating ART as soon as possible after HIV diagnosis has been shown to nearly eliminate HIV sexual transmissions in heterosexual stable discordant couples. Preventive effects of ART were showcased in observational and ecological studies [5, 6] as well as in the landmark HIV Prevention Trial Network (HPTN) 052 trial in which the HIV-positive partners of HIV serodiscordant stable couples were randomized to immediate initiation of ART [7].

Based on such compelling evidence, the World Health Organization (WHO) recommended in 2015 that ART should be offered to all individuals diagnosed with HIV regardless of their CD4 count and clinical staging [35], and the Joint United Nations programme on HIV/AIDS (UNAIDS) proposed the 90-90-90 targets for HIV treatment scale-up by 2020 (namely, that 90% of HIV-infected persons know their status; that 90% of those who know their positive HIV status continue on an efficacious ART regimen; and that 90% of those on ART have undetectable HIV-1 RNA) [9].

Mathematical models have predicted large effects of initiating ART as soon as possible after HIV diagnosis on HIV incidence in the framework of a “Universal HIV testing and treatment (UTT)” strategy, which involves offering regular HIV counselling and testing to an entire population, and ART to all those HIV-infected [10-13]. In a context where HIV funding is flat, obtaining evidence-based data on UTT long-term impact is critical [13, 14]. To fulfil this need, several research projects, including randomized controlled trials in Southern and Eastern Africa, have evaluated or are currently evaluating the field efficacy of UTT on HIV control [15, 17-19, 36]. Among them, the ANRS 12249 Treatment-as-Prevention randomized controlled (TasP) trial was conducted at the Africa Health Research Institute (AHRI) from 2012 to 2016 in rural South Africa, in partnership with a French scientific consortium led by François Dabis at the University of Bordeaux [19].

Given the unprecedented HIV services uptake rates required to achieve the full potential impact of UTT, pressing research questions need to be answered on the feasibility, acceptability, cost-effectiveness and sustainability of the UTT interventions [2]. Such evidence would be key to guide future policy and practice towards optimal wide scale implementation of UTT strategies in the routine health system. My doctorate offers to answer some of those questions. I focused my work on three gaps of the scientific literature, using the TasP trial as an example. First, as there is no “UTT recommendation” per say, no “all-inclusive package of UTT interventions”, it is unclear how the UTT strategy has been understood, defined and implemented in various contexts. It is also unknown how public health care workers (HCW) exposed to UTT understand and claim ownership over UTT interventions. Finally, it is also unknown how individuals exposed to UTT react to the integration of those innovative interventions in their care routine.

Chapter 1 of this thesis describes the HIV epidemic management globally, and more specifically in South Africa. It presents a situation analysis of the HIV epidemic, reviews the empirical evidence, benefits and challenges on the available tools in the fight against HIV and reports on the last achievements and issues of HIV care management from HIV testing to viral suppression. In chapter 2, we describe the problem from which this research stems, the main objective as well as the settings and the research project in which the PhD was embedded (The TasP trial). The third chapter presents the rationale, methods and main results of our original research. It is articulated in three parts: (i) state of the UTT research in sub-Saharan Africa, (ii) views of HCWs regarding UTT, (iii) care trajectories of people living with HIV in a UTT strategy. The last part of this work (chapter 4) discusses the results in the context of other published research and highlights lessons learnt during the PhD that may be relevant for future research.

This PhD is expected to give insights on how a UTT strategy has worked in a close-to-real life setting in a context of a generalized epidemic, and what have been the important aspects of UTT for HCWs and people living with HIV. My PhD exercise is therefore expected to bring valuable information for decision-makers and program planners considering implementing a panel of UTT interventions in national health programs, and guide them into what could be done to improve HIV care.

CHAPTER I

FACTUAL BACKGROUND

In this chapter, we take stock of the global HIV epidemic in order to understand how the infection has burdened the rural South African communities in which the PhD work was performed. We first present a situation analysis of the HIV epidemics. We then review the empirical evidence, benefits and challenges on the available tools in the fight against HIV including ART. We finally report the last achievements and issues of HIV care management from HIV testing to viral suppression.

1 FACTUAL BACKGROUND

1.1. The global situation of the HIV/AIDS epidemic

The human immunodeficiency virus type 1 (HIV-1), a retrovirus [37, 38] was named in 1983 as the causative agent for the Acquired Immune Deficiency Syndrome (AIDS) identified in homosexual men in 1981 [39]. Since its discovery, HIV has infected over 78 million people and caused over 35 million deaths [40], making it one of the most devastating pandemics of recent times [41].

1.1.1. Epidemiology of the HIV/AIDS epidemic

According to UNAIDS estimates for the year 2015, 36.7 million persons are infected with the HIV virus worldwide, with an estimated 2.1 million new infections and 1.1 million deaths that year. Sub-Saharan Africa is by far the hardest-hit region, with 25.5 million people infected, followed by Asia and the Pacific, with a combined total of 5.1 million [34].

The HIV prevalence varies greatly by country. Most countries in sub-Saharan Africa have generalized epidemics (HIV prevalence exceeds 1% of the general adult population) with coexisting "concentrated" epidemics (HIV prevalence exceeds 5% in "vulnerable" sub-populations (e.g., sex workers, men who have sex with men, injecting drug users). The highest rates of HIV infection are in Southern Africa where HIV is hyperendemic (over 15% of the adult population is infected) [1] (Figure 2).

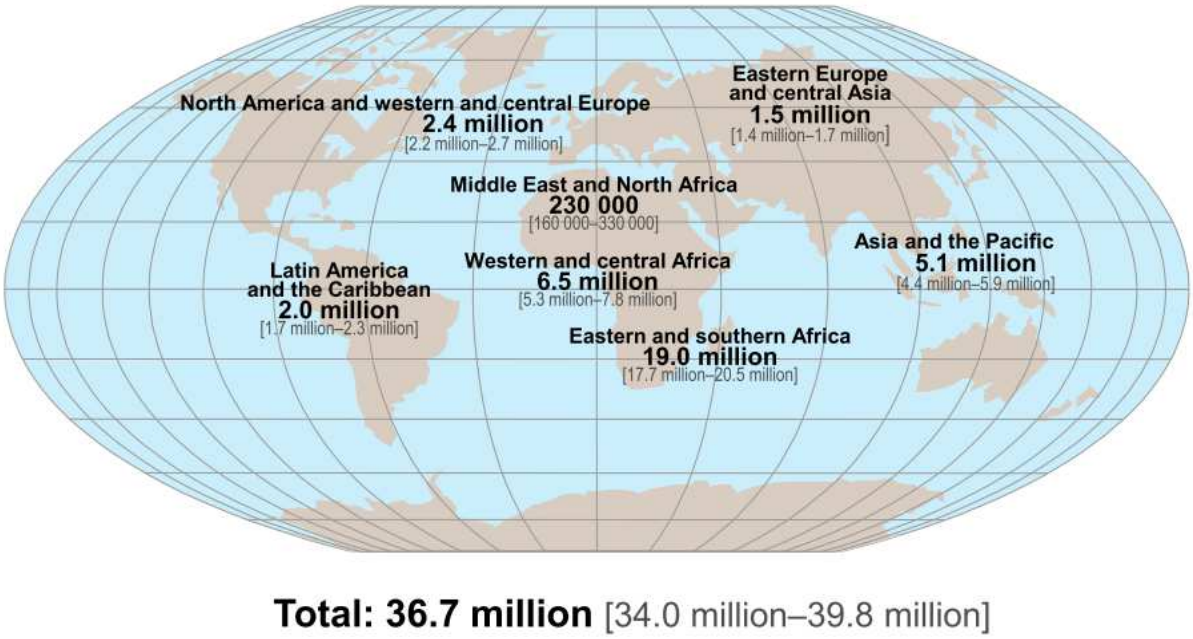


Figure 2: Adults and children estimated to be living with HIV in 2015 [1]

As shown by the graphs in Figure 3, the global epidemic has receded considerably in recent years. The number of deaths from AIDS has fallen 30% from the peak reached in 2005 [1]. New infections are down 33% from 2001. Since 2010, they have decreased in children by 50% but have stabilized in adults [1]. Nonetheless, the number of persons living with HIV continues to rise, as a consequence of the number of new infections remaining higher than number of deaths and the survival of those receiving ART.

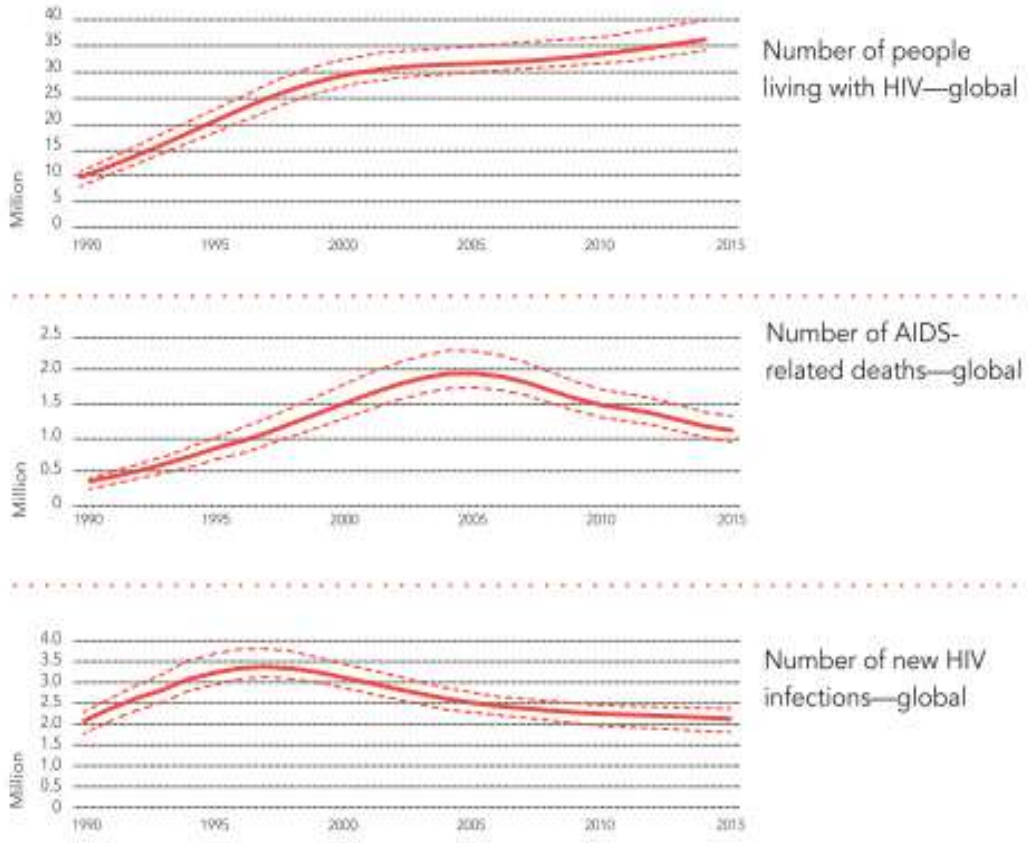


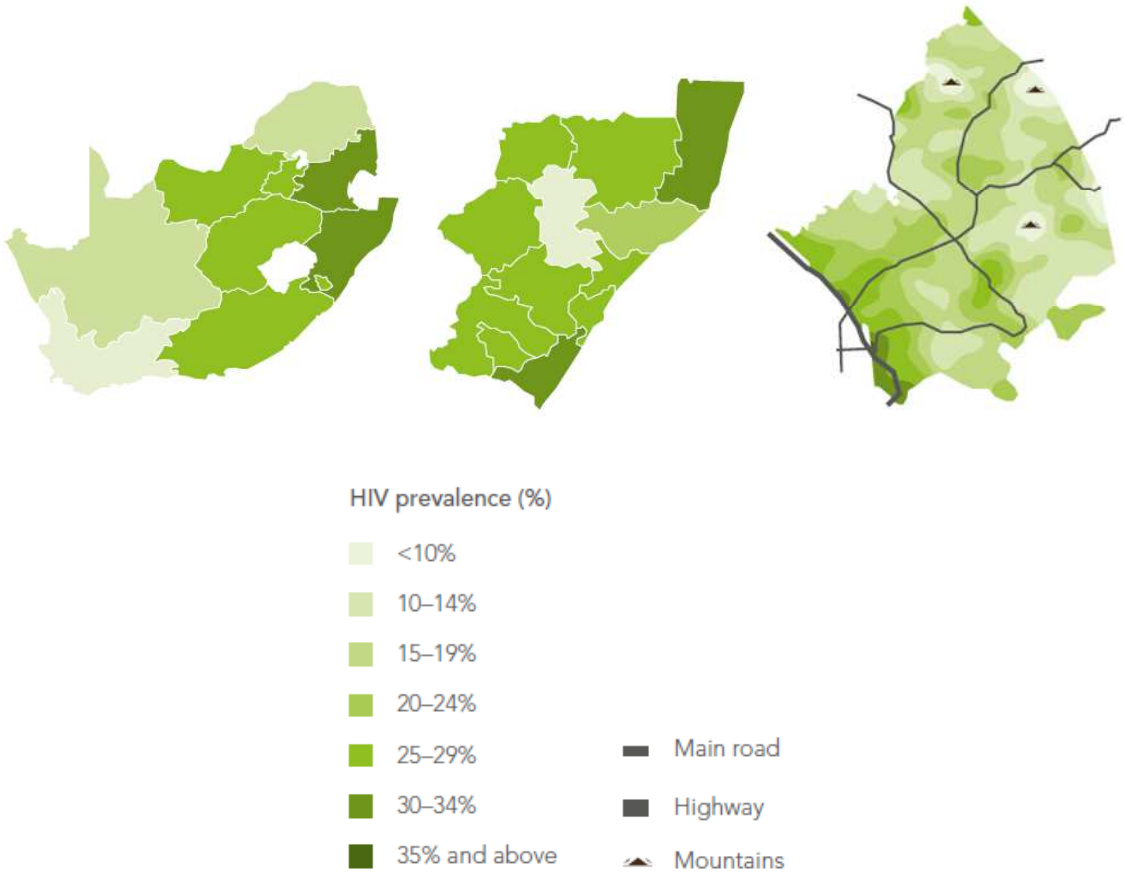
Figure 3: Trends in the number of people living with HIV, new HIV infections, and AIDS deaths, global data for 1990-2015 [1]

1.1.2. The state of the HIV/AIDS epidemic in South Africa

1.1.2.1. A truly generalized epidemic

South Africa has the largest and most severe HIV epidemic in the world, with an estimated 7 million people living with HIV in 2015. In the same year, there were 380,000 new infections while 180,000 South Africans died from AIDS-related illnesses [42]. The rates of opportunistic co-infections associated with HIV are disproportionally high in the country: 60% of people living with HIV are co-infected with Tuberculosis (TB) and TB account for around one in three AIDS-related deaths [43]. Since 2010 the national HIV prevalence has remained virtually unchanged mainly as a result of the national ART-scale up and the subsequent decrease in HIV-related mortality [1].

HIV prevalence is high among the general South African population (19.2% in adults aged 15-49 years) [44], although it varies markedly between provinces. As Figure 4.a. shows, the estimated HIV prevalence among adults differs by as much as three-fold, depending on the province, and is exceptionally high in the KwaZulu-Natal province [44]. Among pregnant women in 2011, it exceeded 30% in all but one of that province's districts (Figure 4.b.). HIV prevalence varies widely even within districts. Figure 4.c. depicts a small, 438-km^2 part of Umkhanyakude district in northern KwaZulu-Natal, that is home to about 87 000 residents. The HIV prevalence among adults in the area averaged 22% but varied drastically depending on the specific area—exceeding 35% in the high-density settlements toward the east, along a major road, but 10% or less in the more remote western parts [45] .



a. b. c.

Figure 4: Variations in HIV prevalence in South Africa (adapted from [46])

a. HIV prevalence by province in South Africa [44]; b. HIV prevalence by district in KwaZulu-Natal province in South Africa [47]); c. Clusters of low and high HIV prevalence in the Northern part of Umkhanyakude district, in KwaZulu-Natal province [45]

1.1.2.2. Epidemic drivers in South Africa

At the beginning of the HIV epidemic, the social, economic, and environmental conditions created by apartheid in South Africa, such as overcrowded squatter settlements, migrant labour, and deliberately underdeveloped health services for black people, provided a favourable

environment for efficient transmission of HIV [48]. Because these historical conditions have continued to define the nature of the HIV epidemic in South Africa, HIV has remained a crucial public health challenge in the post-apartheid era [49].

For now the factors accounting for the substantial differences of HIV prevalence observed between South Africa's provinces are poorly understood. Data repeatedly underscore the importance of heterosexual transmission driving a large part of the generalized epidemic, influenced by several key epidemiological factors such as age, gender, mobility, sexual partner profile, and the presence of other sexually transmitted infections (STIs) [50]. Young women aged 15-24 are considered as the most vulnerable to HIV and therefore as the main drivers of the epidemic. They account for over four times more new infections than men the same age, which represents 25% of the new infections nationally [51].

To better understand the high vulnerability of young women, a recent phylogenetic work has mapped out the infection cycle between men and women of different ages in KwaZulu-Natal [52]. The authors found that teenage girls were infected by men who were, on average, 8 years older. After the age of 24, people typically became infected by partners their own age, with transmission more frequently moving from woman to man. These older men are the same group having sex with the youngest women (Figure 5).

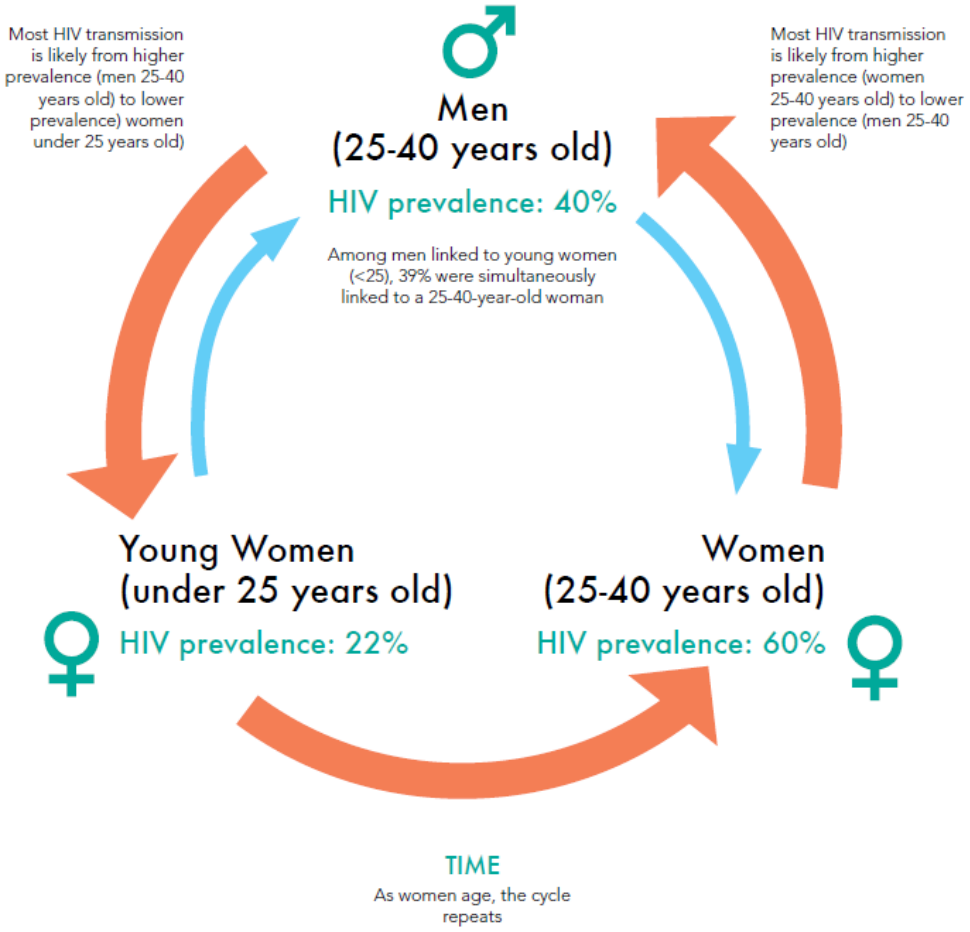


Figure 5: Schematic presentation of the sexual networks of HIV-positive men and women in phylogenetically identified heterosexual transmission clusters, in KwaZulu-Natal South Africa, 2016 (adapted from [52])

The generalized epidemic in South Africa also coexists with “concentrated” epidemics. The South Africa's National Strategic Plan 2017-2022 identifies a number of key affected populations that are at risk of HIV acquisition [53], including men who have sex with men, sex workers, people who inject drugs, children and orphans, and women, adolescent girls. The highest vulnerability of those groups results from a range of factors that reduce their ability to avoid HIV infections. In general, vulnerability factors include lack of knowledge and skills required to protect oneself and others, limited accessibility, quality and coverage of services, and restrictive societal factors, such as human rights violations, punitive laws or harmful social and cultural norms [43, 54, 55].

1.2. The HIV response: prevention and treatment worldwide and in South Africa

The fall in new infections and AIDS-related deaths worldwide and in South Africa in particular has been achieved through a combination of several factors, including a better understanding of the epidemic, bringing changes in the health systems (innovations in prevention and treatment strategies), as well as bringing changes to the law, policy and finances of the HIV response.

1.2.1. HIV Treatment

1.2.1.1. Antiretroviral therapy: successes and limits

The first breakthrough in the field of HIV treatment occurred in 1996 when it was found that triple drug therapy (known as highly-active antiretroviral therapy or HAART) could durably suppress viral replication to minimal levels and enable one's immune system, whose cells are destroyed by the virus, to recover; the body can once again fight against infections (Figure 6) [56].

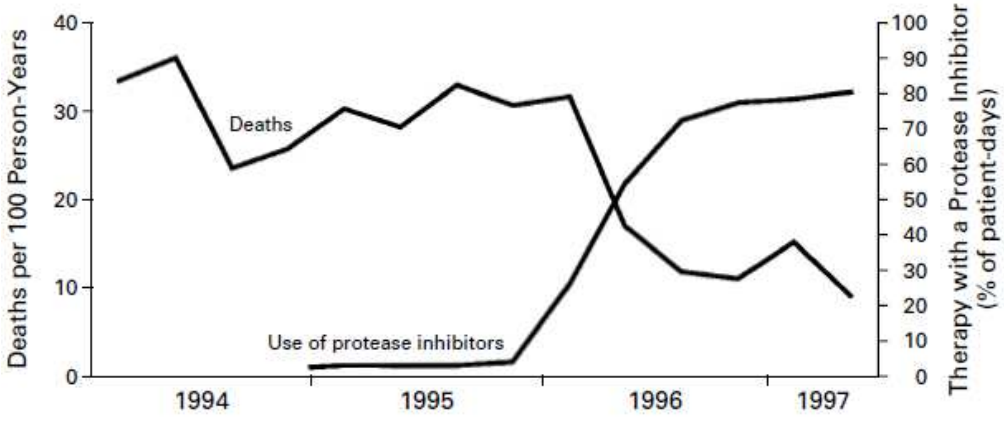


Figure 6: Decrease of HIV disease mortality after the introduction of potent combined antiretroviral therapy [56]

The combination antiretroviral therapy included a protease inhibitor among HIV-infected patients with fewer than 100 CD4+ cells/mm^3, according to calendar quarter from January 1994 through June 1997.

Up to now, more than 20 antiretroviral agents have been licensed, in most cases through an accelerated approval (Figure 7) [57]. Despite these impressive results, issues encountered in medical practices call for the development of new drugs. Currently research efforts are focused on improving safety and/or resistance profile within the existing drug classes, combination therapies with improved adherence (e.g. single-tablet regimens), novel mechanisms of action (e.g. attachment inhibitors, maturation inhibitors, broadly neutralizing antibodies), and

treatment simplification with infrequent dosing (e.g. long-acting injectables). In parallel with ART innovations, research and development efforts focused on agents that target persistent HIV reservoirs may lead to prolonged drug-free remission and HIV cure [58].

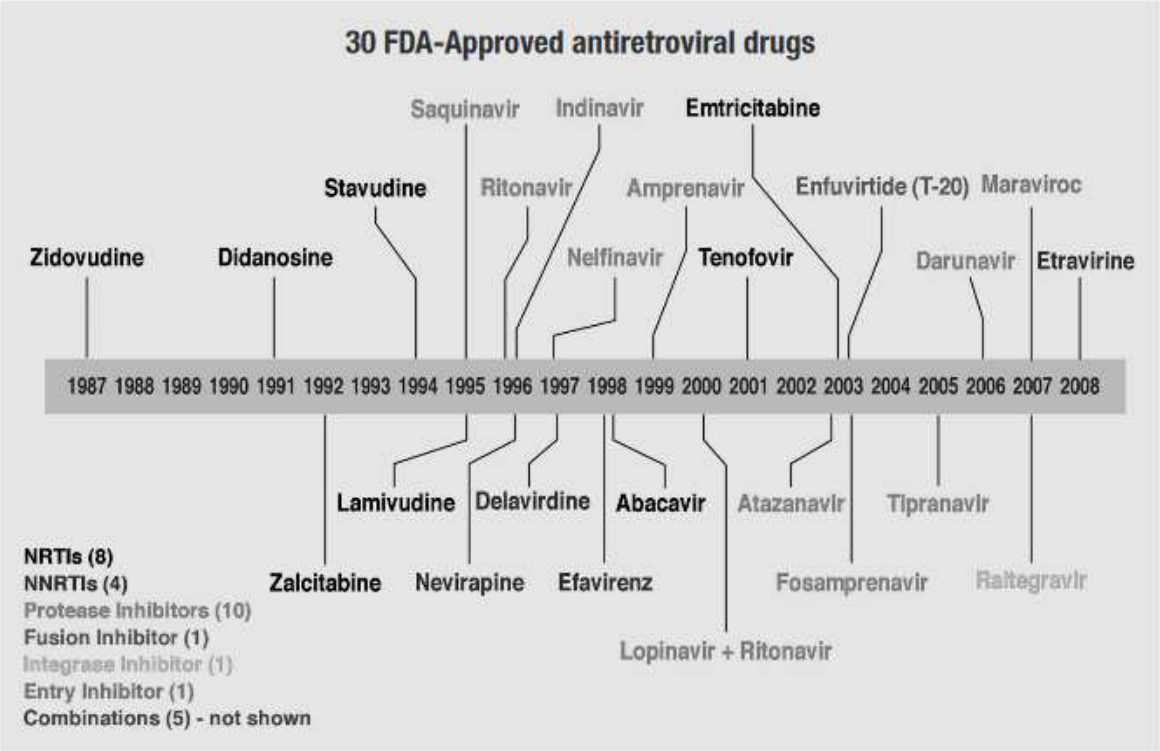


Figure 7: Antiretroviral drugs approved for HIV infection [57]

FDA: United States food and drug administration; NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors

1.2.1.2. Evolution of international guidelines for ART initiation

Results of research studies have made major contributions to optimizing ART and helped form the basis of WHO guidelines for initiating ART (Figure 8). In 2002, WHO recommended ART for HIV-infected patients in moderate and advanced stages of infection (CD4 count < 200 cells/μL) } a CD4 count lower than 350 cells/μL, when most people are still asymptomatic [59, 60], with additional evidence of ART impact on HIV mortality, disease progression and comorbidities (TB) [61, 62]. In 2013, WHO guidelines have suggested to expand the ART eligibility criteria at CD4 count <500 cells/μL [63]. The recommendation was hinged on the premise that untreated HIV may be associated with the development of non-AIDS-defining conditions [64-66] and that initiating ART earlier reduces such events and improves survival, as well as the results from the HPTN 052 trial demonstrating the effectiveness of ART in reducing HIV transmission in stable sero-discordant couples [7]. A further supporting argument was that currently available ART regimens have become less toxic and easier to take and the cost of providing ART is becoming cheaper [67]. In 2015, WHO recommended treatment for all people living with HIV regardless of CD4 count and clinical stage [35]. It was based on the results of two randomised trials, TEMPRANO and START on the individual clinical benefits of ART. They showed that starting ART early in the course of the HIV infection decreased HIV morbidity and disease progression without increasing severe adverse events [3, 4]

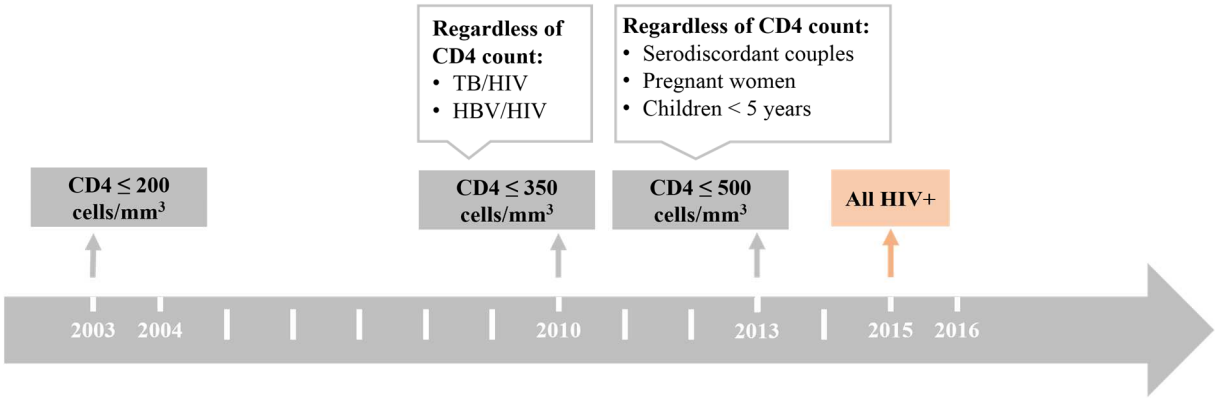


Figure 8: Evolution of antiretroviral treatment guidelines according to the World Health Organization

ART: antiretroviral treatment, CD4: CD4 count (cells/mm^3); HIV: human immunodeficiency virus, HIV+: people living with HIV, TB/HIV: co-infection with Tuberculosis and human immunodeficiency virus, HBV/HIV: co-infection with Hepatitis B virus and human immunodeficiency virus

1.2.1.3. Worldwide ART coverage

As WHO started providing ART recommendations, countries gradually followed the guidelines. Yet, it was then widely felt that ART was too expensive and complex for low- and middle-income countries, and so a massive scale-up did not begin in most of these countries until the WHO launched its '3 by 5' initiative (Treating 3 million by 2005), and sizeable funding mechanisms, such as the Global Fund to Fight AIDS, TB and Malaria and the US President's Emergency Plan for AIDS Relief (PEPFAR), came into existence. A pivotal enabler of the scale-up was a steady lowering of drug prices through entry of generic. As the last WHO guidelines issued in 2015 recommend that all individuals living with HIV should start treatment, countries are gradually following those recommendations (Figure 9) [68].

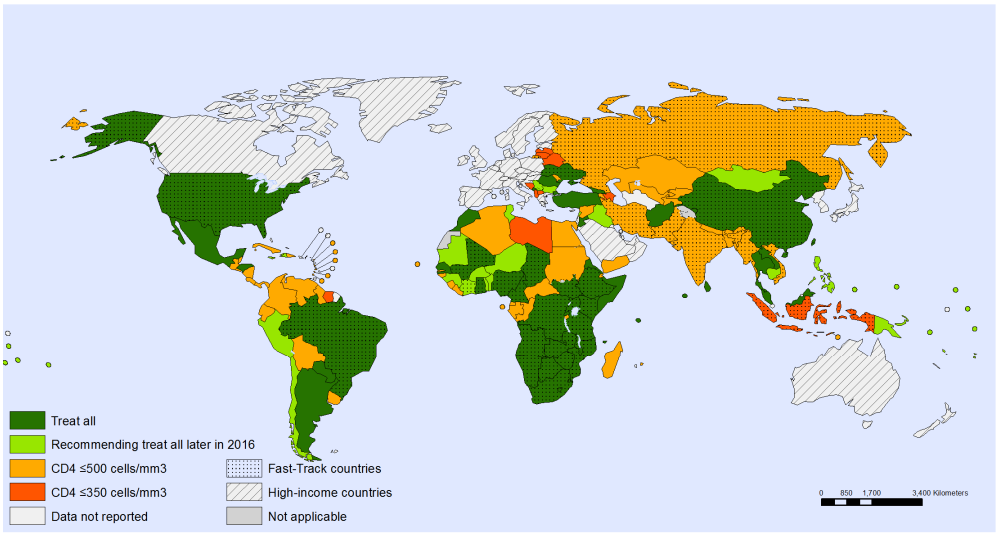


Figure 9: Adoption of the "treat all" WHO recommendation among adults and adolescents living with HIV in low- and middle-income countries, 2016 [68]

Scale-up of ART has been on a Fast-Track trajectory that has surpassed expectations. Global coverage of ART reached 46% of adults [43–50%] at the end of 2015. Gains were greatest in the world's most affected region, Eastern and Southern Africa [69] (Figure 10). Coverage increased from 24% [22–25%] in 2010 to 54% [50–58%] in 2015, reaching a regional total of 10.3 million people. Improvements in ART coverage are largely responsible for the 26% decline in AIDS-related deaths globally since 2010, from an estimated 1.5 million [1.3 million–1.7 million] in 2010 to 1.1 million [940 000 –1.3 million] in 2015 [69] (Figure 10).

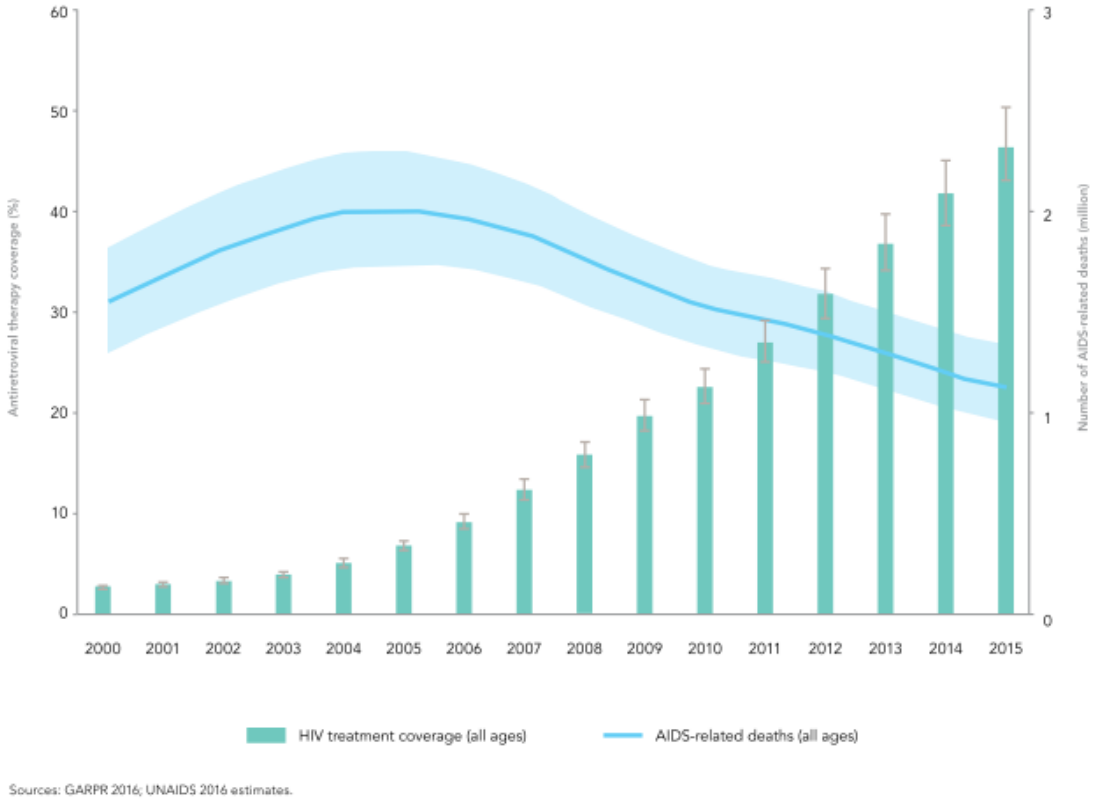


Figure 10: Antiretroviral therapy coverage and number of AIDS-related deaths, global, 2000-2015 [69]

UNAIDS 2015 definition of antiretroviral coverage: proportion of individuals accessing and receiving ART a point in time. The numerator is the number of people who receive the ART and the denominator is the number of individuals who are eligible to receive the ART at the same point in time [70].

1.2.1.4. ART coverage in South Africa

For several years since the beginning of the HIV epidemic, the South African Government's response has been marked by denial, lack of political will, and poor implementation of policies and programmes[49]. Nonetheless, there have been notable achievements in disease management, including substantial improvements in scale-up of free ART and the national implementation of a task-shifting programmes which entitles nurses to initiate patients on ART [49]. In 2007, the first Strategic Plan for South Africa for HIV-AIDS has been developed through an inclusive process involving scientists and activist [71]. Since then, the country has been following up WHO recommendations with some delays [72] (Figure 11). With regards to treatment, the ART coverage has been increased by 70% since 2010, leading to the largest

national treatment programme in the world with 3.54 million of people on treatment in 2016 [1]. These investment are now beginning to bear fruits with the number of new infections and HIV-related deaths in South Africa declining [44]. ART coverage is likely to increase substantially with the most recent South African HIV treatment guidelines recommending immediate offer of ART in individuals diagnosed HIV-positive regardless of CD4 counts [73].

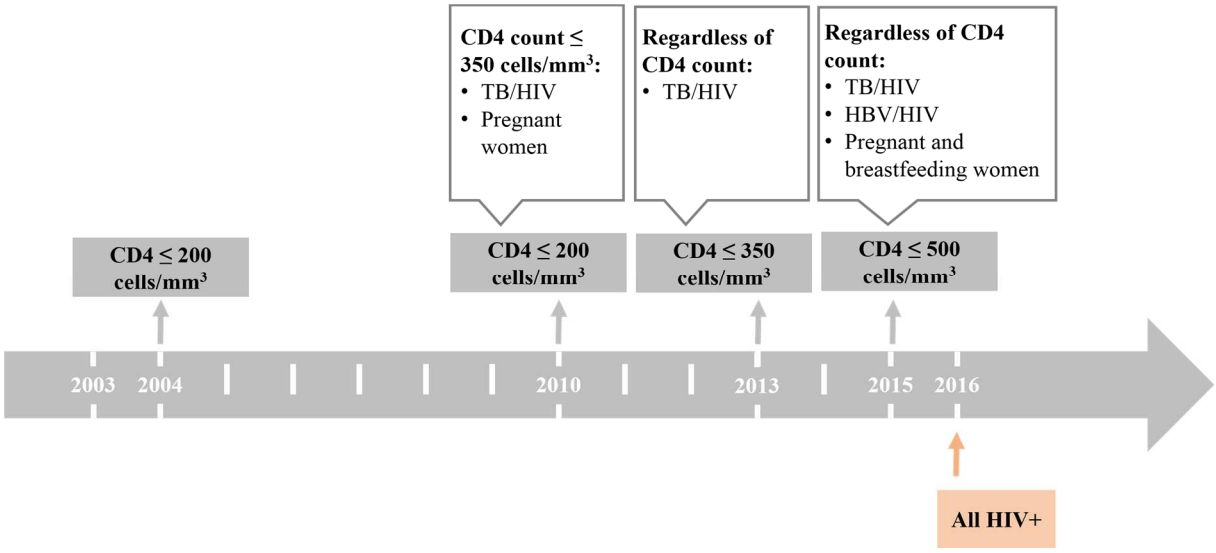


Figure 11: Evolution of antiretroviral treatment guidelines according to the South African guidelines

ART: antiretroviral treatment, CD4: CD4 count (cells/mm³); HIV: human immunodeficiency virus, HIV+: people living with HIV, TB/HIV: co-infection with Tuberculosis and human immunodeficiency virus, HBV/HIV: co-infection with Hepatitis B virus and human immunodeficiency virus

1.2.2. HIV prevention

Prevention efforts, have played an important role in limiting new infections [74]. As shown in Figure 12, they include human rights-based and evidence-informed behavioural, biomedical [75] and structural strategies. To achieve high coverage for a measurable reduction in population-level HIV transmission, they are often combined in health programs, therefore labelled "combination HIV prevention" and their use vary depending on the targeted subpopulations (Figure 12) [76, 77].

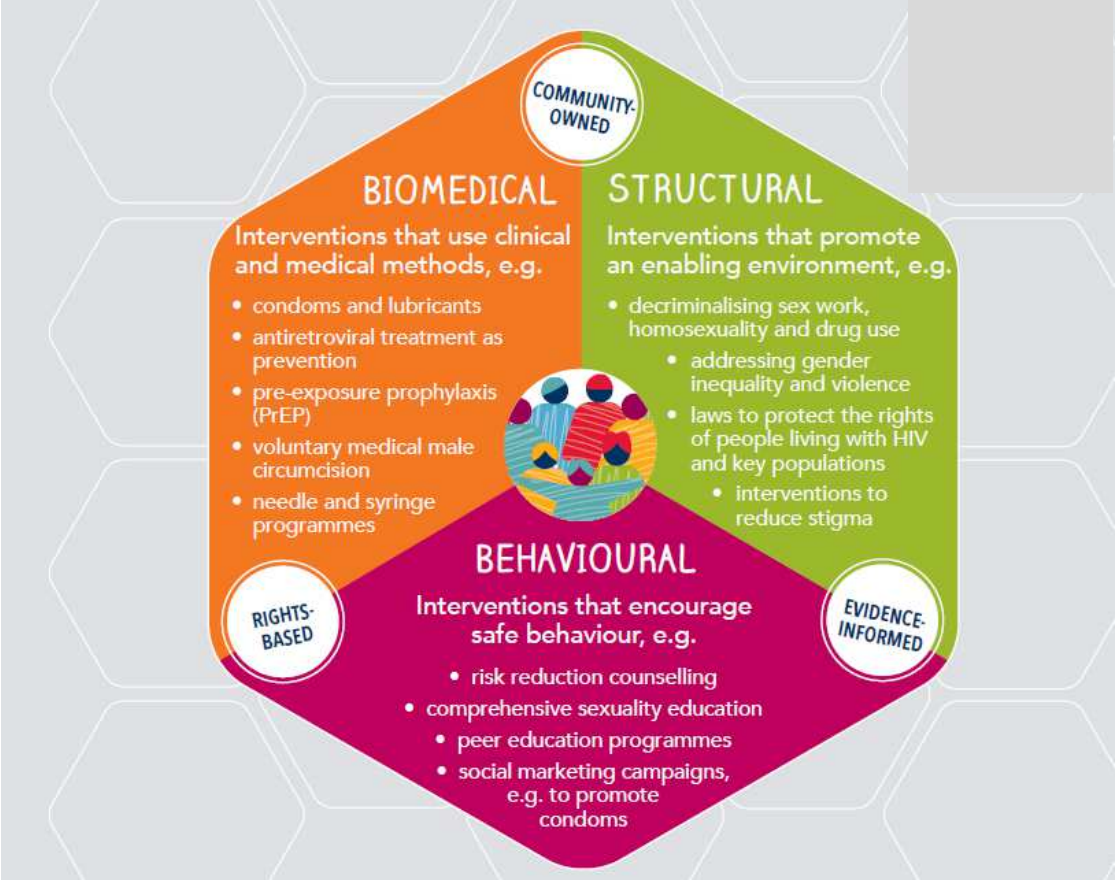


Figure 12: Elements of combination HIV prevention [77]

1.2.2.1. Structural HIV prevention

The response to HIV also recognizes that human behaviours are deeply embedded in, and shaped by, underlying social, economic and legal-political structures promoted. Therefore, reducing HIV risk requires changes in broader structural elements (e.g. economic opportunities, social norms and gender roles, legal freedoms) [78].

Progress in incorporating structural approaches into HIV prevention has been limited mainly because of a lack of consensus on definition and implementation. As structural approaches address deeply entrenched social, economic, and political factors that are difficult to change, they are commonly viewed as long-term initiatives that go beyond the scope of HIV prevention. An example of structural approaches in South Africa is the intervention with microfinance for

AIDS and gender equity (IMAGE) project. The project sought to reduce gender-based HIV vulnerabilities, such as sexual violence, women's economic dependency on men, and women's lack of in-depth information about HIV and its transmission. IMAGE addressed these three issues by partnering with a local microfinance institution to enable women to pursue microenterprises, while offering participants HIV education and creating opportunities to discuss and mobilise local action against gender-based violence [79]. The IMAGE project did make important findings. It estimated that over 2 years, levels of intimate partner violence were reduced by 55% in the intervention group relative to the reference group. Additionally, there was evidence that the intervention improved household wellbeing, social capital, and empowerment. Disappointingly, however, there appeared to be no direct effect on HIV incidence [79].

1.2.2.2. Behavioural HIV prevention

Behavioural interventions focus on changes in sexual behaviours. Examples are delaying onset of first intercourse, decreasing the number of sexual partners, increasing the number of sexual acts protected, counselling and testing for HIV including repeat HIV testing, encouraging adherence to biomedical HIV prevention strategies, decreasing sharing of needles and syringes and reducing substance use.

Behavioural interventions have been shown to have some impact ion HIV transmission, but the lack of sustainability of such strategies makes it difficult for them alone to confer substantial effects at a population level [80]. A 2010 review of behavioural intervention trials, with HIV incidence as main outcome, showed no significant reduction in HIV incidence in any of the nine randomised-controlled trials studied [81]. An example of behavioural interventions in South Africa is the Project Accept (HPTN 043). This cluster-randomised trial evaluated whether a community-based versus a facility-based HIV counselling and testing could reduce HIV incidence. The trial showed no significant reduction in HIV incidence overall (relative risk [RR] 0·86, 95% CI 0·73–1·02) although there was a significant reduction in HIV incidence in the sub-group of women > 24 years of age (RR=0·70, 0·54–0·90) [82].

1.2.2.3. Biomedical HIV prevention

1.2.2.3.1 Non ART-based biomedical tools

Condoms

In a 2002 pooled analysis, the consistent use of condoms was associated with an 80% reduction in HIV incidence [83]. Condoms continue to be an important element of any comprehensive HIV prevention strategy.

In South Africa, male condoms are widely available and the female condom programme is one of the biggest and most established in the world [84]. However, in a 2012 survey, 53% of participants had never used condoms [51]. This study also showed a decline in condom use over time. In 2012, 68% of 15-24 year old males reported having used a condom during their last

sexual encounter, versus 85% in 2008. Condom use among men aged 25-49 also decreased over the same period, from 44% to 36%.

Voluntary medical male circumcision

Voluntary medical male circumcision (VMMC) is one of the most powerful and cost-effective HIV prevention tools at hand. Three randomised controlled trials conducted in South Africa, Uganda and Kenya provided evidence that VMMC is effective in reducing woman-to-man transmission [85-87]. In a pooled analysis, VMMC was shown to reduce HIV acquisition by heterosexual men by between 38%and 66% over 24 months [88].

VMMC is now practiced in countries with extremely high prevalence rates where few men were circumcised traditionally [1]. South Africa scaled it up in 2010, driven by a broader intervention of the WHO and the UNAIDS to encourage VMMC in priority countries [89]. It has been mostly well received by the population, as evidenced in a study conducted in a rural community in KwaZulu-Natal province in 2005 (51% of uncircumcised men and 68% of women favoured male circumcision of themselves or their partners) [90], and in a study conducted in the Western Cape province in 2015 (89% of participants believed circumcision was an acceptable practice) [91]. The 2016 circumcision rate remains stable but high lready with 50-79% of eligible men reached nationally [1].

Treatment of sexually transmitted infections

Substantial evidence exists from observational studies suggesting an increased risk of HIV acquisition when infected by curable sexually transmitted infections (STIs) and genital herpes [92, 93]. Based on such observations, multiple randomized clinical trials have investigated treatment of those infections to reduce HIV transmission and acquisition, however none showed any significant effect [94].

Yet, as compelling biological and epidemiological evidence that STIs are co-factors for HIV acquisition and transmission remain [95], and STI contribute largely to the global burden of disease in South Africa [96], the national strategic plan for HIV and AIDs also includes STI management [53].

Safe blood transfusion and clean injection equipment

HIV can be acquired through blood exchange, either by receiving a contaminated blood transfusion or by exchanging used syringes with infected individuals.

Progress towards improving safe and adequate supplies of blood is being made worldwide. Between 2010 and 2015, two cases of HIV transmission were recorded in blood transfusion in South Africa. Since then, no case were reported [97].

The importance attributed to unsafe medical injections in the transmission of HIV in sub-Saharan Africa has been minimized by the enormous attention given to sexually transmitted HIV [98]. In 2008, studies in South Africa highlighted cases of HIV transmission in children receiving immunizations in public health facilities; interviews with health care workers reported reusing syringes [99]. Current South Africa efforts to eliminate re-use of syringes focus on programs to improve providers' practices and support the procurement of appropriate injection commodities [100].

Harm reduction efforts such as opioid substitution therapy (OST) and needle and syringe programs have shown to be effective at reducing HIV in people who inject drugs [101]. Despite the large numbers of people who inject drugs and the high risk associated with injecting drug use, coverage and access to those services remains sub-optimal [102]. In South Africa, it is estimated that there are 67,000 PWIDs [103] and that HIV prevalence among them is 19.4% [104]. To date, no government-funded needle and syringe programmes or OST for people who inject drugs exist in the country and the cost of OST medications remain very high [105].

HIV vaccines

Research into a preventive vaccine to reduce susceptibility of HIV-negative individuals had been under way for the last twenty years and continues [106, 107]. Most vaccine prototypes developed until now have proven to be ineffective or at best partially effective - VAX004 (North America and the Netherlands [108], VAX003 (Thailand) [109], Step (North and South America, the Caribbean and Australia) [110], Phambili (South Africa) [111] and HVTN 505 (USA) [112]. In a large RCT in Thailand (n=16,402), the RV144 vaccine trial showed a slight vaccine efficacy of 31% (95% CI, 1.1 to 52.1) after 3.5 years [56]. To date, this remains the only vaccine trial to demonstrate some protection against HIV acquisition. Two phase-2b vaccine trials are currently enrolling participants. They evaluate the safety and efficacy of vaccine candidates in reducing HIV infection in women (HVTN 703/HPTN 081) (ClinicalTrials.gov Identifier: NCT02568215) or men who have sex with men/transgender women (HVTN 704/HPTN 085) (ClinicalTrials.gov Identifier: NCT02716675).

In 1999 the South African government established the South African AIDS Vaccine Initiative to co-ordinate and support the development and testing of HIV vaccines in South Africa. In 2013, such initiative was included as a lead programme of the South African Medical Research Council [113]. It currently funds 10 projects [114].

1.2.2.3.2 ART-based biomedical tools to prevent HIV acquisition

Studies have shown that ART could be used not only by HIV-positive individuals to improve their own health but also by HIV-negative individuals to prevent them from acquiring HIV.

ARV for post-exposure prophylaxis

The use of ART after being potentially exposed to HIV to prevent becoming infected is commonly known as Post-exposure prophylaxis (PEP). The evidence base for PEP rely heavily on preclinical data and cohort data (mainly following occupational injury) [115]. It is unlikely that this will change considerably, as randomised studies of different drug regimens for PEP are not feasible owing to the complexity of exposure, low event rate, and inability to ethically have a placebo group.

The need in South Africa for PEP cannot be underestimated. As the country has the largest number of people living with HIV and high rates of sexual violence, sizeable numbers of people are at risk of being infected with the virus [116]. PEP has been available in South Africa since the 1990s [117]. Understanding of how effective it can be has been growing both amongst health providers and people who may need it. However, as in other countries, compliance with the PEP drug regimen remain one of the biggest challenges [118].

ARV for pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) is the use of ARV drugs by HIV-negative people before potential exposure to the virus to reduce their risk of HIV infection. Proof-of-concept that PrEP protects against sexual HIV acquisition in both men who have sex with men and heterosexual populations at high risk for acquiring the virus has been demonstrated in four clinical trials - CAPRISA 004 [119], iPrEx [120], TDF2 [121], and Partners PrEP [122]. Reduction in relative risk (RRR) of HIV seroconversion ranged from 39–75% in the intention-to-treat comparisons and 90–92% among those using the study medication, as measured by levels of drug in blood. The efficacy of continuous PrEP has been confirmed in the PROUD study [123]. The efficacy of intermittent PrEP has been shown in the IPERGAY study [124] and the HPTN067/ADAPT study did not show significant difference in HIV incidence between continuous and intermittent PreP [125]. Importantly, however, two trials - FEM-PrEP (testing Emtricitabine / Tenofovir) [126] and VOICE (testing Tenofovir and daily tenofovir gel) [127]- failed to demonstrate HIV protection with PrEP, with low adherence to daily use of PrEP the leading hypothesis for lack of efficacy. The PrEP was well tolerated in all studies, and the evolution of HIV drug resistance has been low. Compensatory increased sexual risk behaviour was not observed in recent studies [128].

South Africa became the first country in sub-Saharan Africa to fully approve oral PrEP. In June 2016, PrEP was rolled out in 11 selected clinics in 5 provinces. In November another clinic was added, to create a total of 12 implementing sites in 2016 [129]. The model is initially intended for sex workers, who have the highest HIV prevalence in South Africa and face high levels of stigma and discrimination [130].

1.2.2.3.3 ART-based biomedical tools to prevent HIV transmission

Research has shown that ART used by HIV-positive individuals not only improve their own health but also prevent them from transmitting HIV. Research has shown that ART can reduce the amount of virus (viral load) in the blood and other bodily fluids (such as semen, vaginal and rectal fluids or breast milk) to undetectable levels, and that there is a dose-response link between viral load and HIV transmission [131].

ART to prevent mother-to child transmission

HIV can be transmitted from the mother to her child during pregnancy and birth through blood, or postnatally through breast milk. There is mounting evidence from randomized trials of the safety and efficacy of ART in preventing HIV transmission from an infected mother to her child, where the mother is undergoing treatment [132].

WHO recommends lifelong ART for all pregnant and breast-feeding women living with HIV [133]. In 2001, the South African government was ordered by the court to develop a fully capable and effective national programme to reduce mother-to-child transmission by the following year. The government challenged the court order, but was unsuccessful. In 2002, the national Prevention of mother-to-child transmission of HIV (PMTCT) programme commenced [134]. Since then, huge progresses have been made, bringing the risk of infant HIV infection down to 1.4% in 2015 [135].

ART to prevent HIV individual transmission among serodiscordant couples

The preventive effect of antiretroviral (ARV) drugs on HIV transmission among serodiscordant couples where the infected member is undergoing treatment has been documented in 11 observational studies (Figure 13) [136]. Rates of HIV-1 transmission to partners were generally higher in low-income than high-income countries. Possible explanations included differences in methodology, rates of monogamy, rates of circumcision, differences in the stage of the HIV-1 epidemic or the proportion of symptomatic cases, patterns of sexual behavior, prevalence of other STIs, and variations in viral strains. The only randomised trial, which was multicentre (HPTN 052) and recruited 1763 stable serodiscordant couples from nine countries, including South Africa, reported initial findings in 2011 [137]. HIV infected individuals with CD4 counts between 350-550 cells/mm^3 and in a stable relationship with an uninfected partner were randomly allocated to receive ART immediately (early therapy) or delayed until CD4 count decreased below 250 cells/mm^3 or development of clinical symptoms (deferred therapy). The result of this study was released early because of clear efficacy of ART in preventing transmission in the early therapy arm. The updated results published in 2016 showed that the efficacy of ART in preventing transmission to sexual partners was durable. Out of a total of 46 linked seroconversions, three occurred in the early therapy group after a median follow up of 5.5 years amounting to a risk reduction of 93%; HR = 0.07 (95% CI 0.02-0.22) [137].

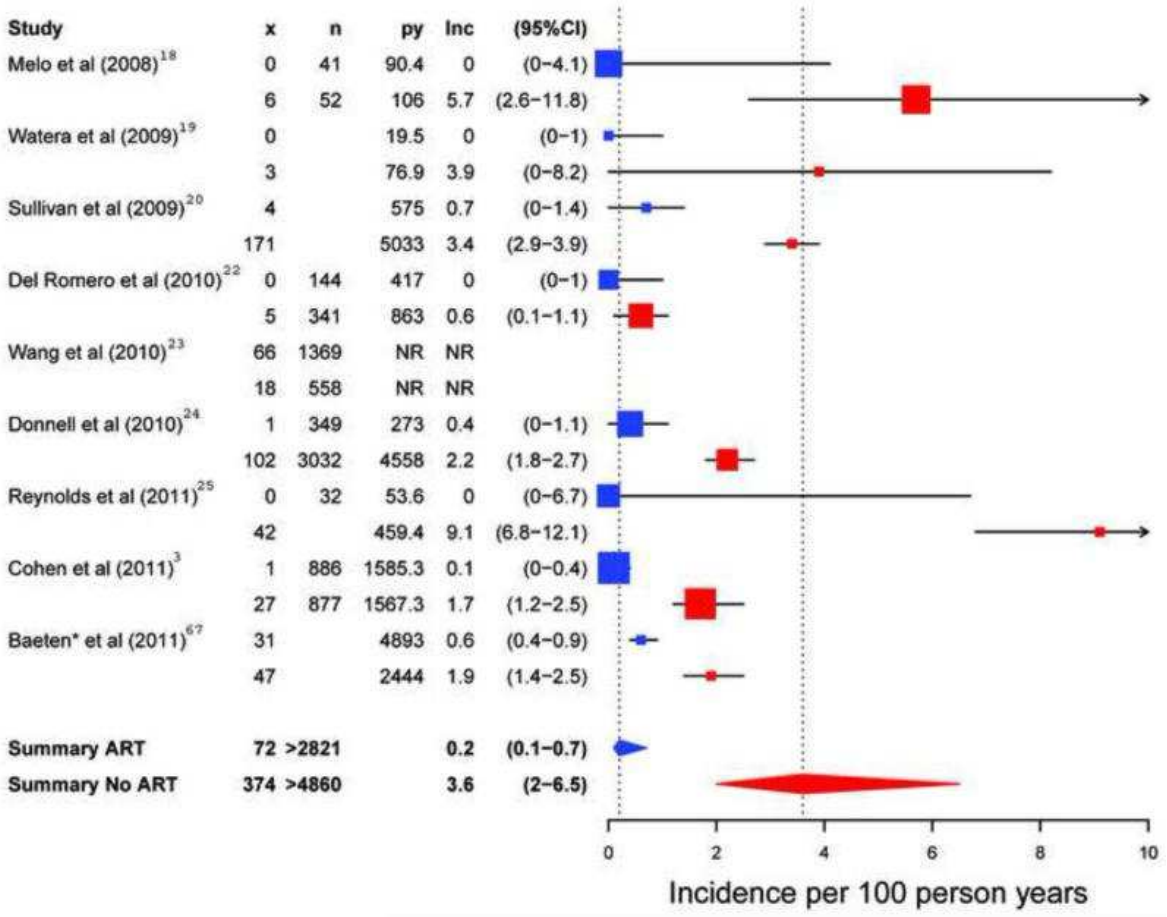


Figure 13: Forest plot summary of HIV-1 incidence rate estimates per heterosexual partnership for ART-stratified studies, with 95% confidence intervals [138].

The first row for each study denotes couples where the index was receiving ART (forest plot boxes in blue); the second row denotes couples with no ART received (forest plot boxes in red). Size of boxes is proportional to number of couples, except for Watera et al 2009 and Sullivan et al 2009, which do not provide these data. Baeten et al refers to ART for the initially uninfected partner rather than the index (pre-exposure prophylaxis) and is shown in the figure but has not been included in the summary estimates. Inc indicates per partnership HIV-1 incidence rate per 100 person-years; n, number of HIV-1 discordant couples; NR, not recorded in publication; x, number of HIV-1 transmitting couples.*

Based on the accumulating evidence, the Swiss commission for HIV/AIDS authored in 2008 a statement to say that HIV+ individuals, on effective ART, with undetectable viral load for at least 6 months and without STIs, are sexually non-infectious [139]. Later on, WHO recommended treatment for all HIV+ individuals in serodiscordant couples in 2012 [140] and for all people living with HIV in 2015 [8]. South Africa has been among the first countries in Africa to formally adopt this policy in September 2016, marking a major policy shift that will move the world faster towards the global 90–90–90 treatment target [141]. Yet, preventive benefits of ART would only be obtained if PLWH take their medication as prescribed, and regularly visit health centres to monitor their viral load and make sure they stay undetectable. The population benefits of ART to prevent transmission remain to be proven.

ART to prevent HIV transmission at population-level

There are various levels of evidence of UTT effectiveness. First, mathematical models suggest that with universal, repeated screening for HIV (to identify infected persons as early as possible) and immediate treatment for all HIV-positive persons, the epidemic could be overcome in 30 to 40 years' time in such countries as South Africa. The first model was developed by Granich and colleagues in 2009 [11] (Figure 14). It required people being tested yearly for HIV, and universal treatment for all HIV+ individuals. Since then, multiple studies have modeled the population impact of UTT [10]. They agreed on the preventive effect of the increase of ART coverage on HIV incidence and that the impact was variable. A more recent model using STDSIM, calibrated to the actual data in the sub-district in which my PhD research was done, showed that it would be possible to reduce prevalence from a peak of 24% in 2015 to 14% in 2040 and incidence from 2.6/100 person years in 2010 to 1.5/100 person years in 2040 if ART is started at CD4 count ≤ 350 cells/mm^3 [142].

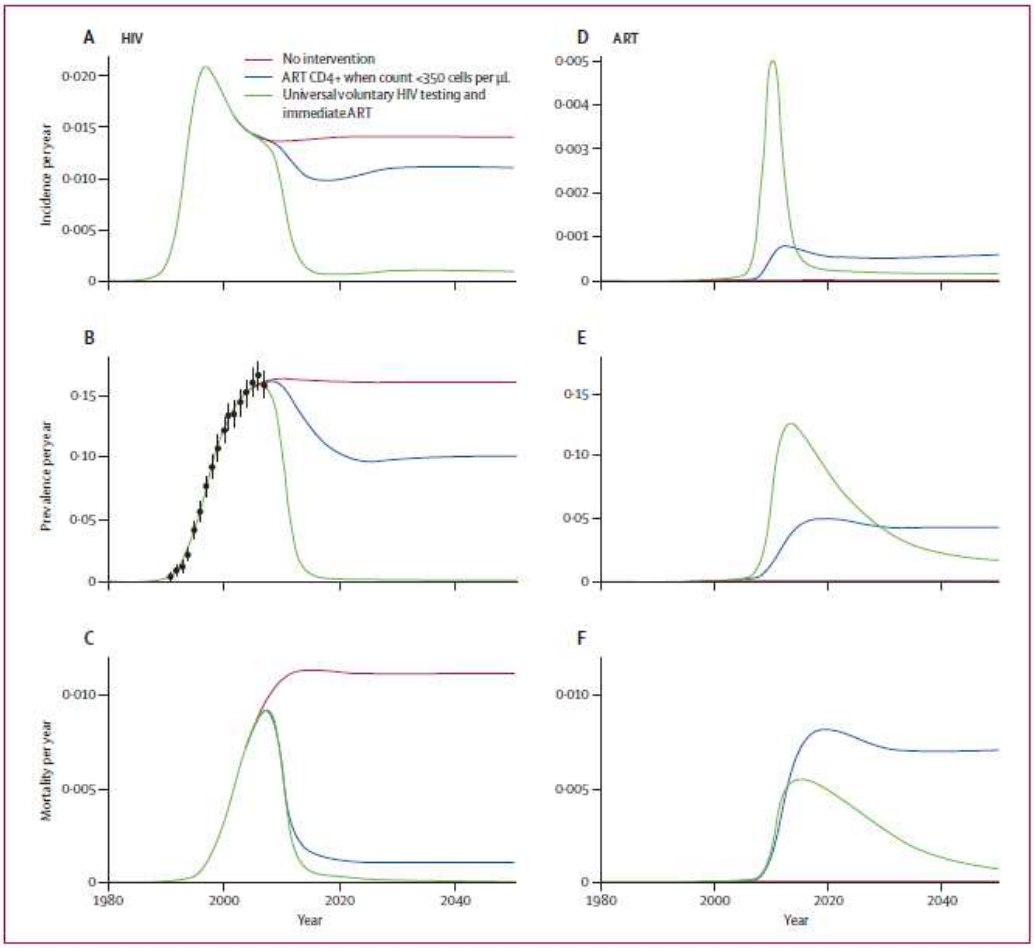


Figure 14 : HIV incidence (A), prevalence (B), and mortality (C) and the incidence (D), prevalence (E), and mortality (F) of people placed on antiretroviral therapy (ART) [11]

Data are proportions of adolescents and adults aged 15 years and older. Left panels, A−C, show HIV incidence, HIV prevalence, and mortality under the three scenarios. In B, data points with error bars give estimated prevalence of infection in adults derived from South Africa antenatal clinic data.35 Right panels, D−F, show incidence of ART—ie, the rate at which people start ART—the proportion of people receiving ART, and the mortality in those receiving ART.

Then, ecologic studies have shown that the increase of the use of ART was associated with a decrease of new diagnoses of HIV [143-146]. Other studies did not show such ecologic relation (United Kingdom, Australia, USA, and Netherlands) [147-150]. A cohort study undertaken in the area of my PhD research has shown that the decrease of the individual risk of HIV acquisition was associated with an increase of the ART coverage in the nearby community [6]. It estimated that an HIV-uninfected individual living in a community with ART coverage of 30 to 40% was 38% less likely to acquire HIV than someone living in a community where ART coverage was <10%. This is the only study to have shown an association between an increase in ART coverage and a decrease in HIV transmission in real-life setting at the population level. Other cohort studies have shown no decrease of HIV incidence on the study period [151].

Finally, several randomized controlled trials (RCTs) have been launched in the previous five years to investigate the effectiveness of UTT in the general population and among selected populations in sub-Saharan Africa (i.e., PopART in South Africa and Zambia, TasP ANRS 12249 in South Africa, BCPP in Botswana, SEARCH in Kenya and Uganda and MaxART in SwaZiland) (Figure 28). Overall, over a million of people were enrolled in those trials. Apart from the ANRS TasP trial, which has reported its main findings, the others are still in progress. The more in-depth analysis of the content of these trials forms part of my PhD work (see Chapter III)

1.2.3. Funding of the response to the HIV/AIDS epidemic

At the end of 2015, US$ 19 billion was invested in the AIDS response in low- and middle-income countries, with domestic resources constituting 57% of the total resources [1]. Recent updated UNAIDS estimates indicate that US$ 26.2 billion will be required for the AIDS response in 2020, with US$ 23.9 billion required in 2030 [1].

South Africa largely funds its HIV and AIDS programmes domestically, only receiving 20% of its HIV funding from external sources [72]. However, based on its National Strategic Plan 2017-2022 targets, the gap between funding requirements and available funding for HIV is expected to grow. This is due in part to the country's middle-income status which is leading to a reduction in funding from external donors. Its commitment to enrol people who test positive for HIV onto treatment immediately after diagnosis may also become a factor [69]. In recent years South Africa has been working hard to negotiate better prices for ARVs, having previously been paying more than most other low and middle income countries despite having the world's largest procurement programme. In 2013, through a more competitive bidding process, South Africa managed to reduce the cost of buying ARVs to the lowest price anywhere in the world. This resulted in a 53% reduction in spending on ART for South Africa [69]. Mathematical models suggest that, the most recent South African HIV treatment guidelines recommending the provision of ART to all individuals diagnosed HIV-positive may significantly reduce costs while reducing the HIV burden [152].

1.3. The HIV care cascade

1.3.1. Framework of the HIV care cascade

1.3.1.1. Definition and international targets

Over the past decade, the concept of the "cascade of care" has become a standard way to monitor HIV care programmes [153-155]. It describes the consecutive stages through which people with HIV pass, including HIV testing, knowledge of HIV status, linkage to initial care, long-term retention in care and treatment adherence (Figure 15). Because each stage in the cascade depends on the previous stage, missing one stage will in general result in failure to fully benefit from ART. The cascade has helped quantify losses of patients from care, identify the points of greatest attrition [156, 157], highlighting that they differ from country to country and even within the same country, depending on factors such as the demographic profile of the population [158, 159]. At population level, failure along the cascade results in excess deaths [160, 161], missed opportunities for preventing sexual transmission of HIV [131], and substantial economic and social costs (e.g. productivity losses, increased healthcare costs, households impoverishment) [162, 163]. As evidence supporting earlier ART initiation and treatment as prevention accumulates, identification of failure points along the cascade is becoming more important in order to characterize these bottlenecks for the purpose of prevailing them.

To guide the efforts towards closing up the gaps in the care cascade, UNAIDS developed in 2014 the 90-90-90 targets for 2020, namely that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive ART and 90% of all people receiving and sustaining ART will have viral suppression [9]. The 90-90-90 targets aim for a decrease in new HIV infections by nearly 90%, and AIDS-related deaths by 80%, by 2030 (Figure 16). UNAIDS estimated that, in 2015 in the world, 60% of people living with HIV knew their HIV+ status, 46% of those were on ART and 38% of those on ART were virally suppressed (Figure 15). As each country aims to compute those cascade estimates, it is important to note that, even though they present valuable information for planning effective interventions, they do not capture entirely the reality of the situation. The cascade appears as a linear process, and the reality is rather that individuals are cycling in and out of care [30]. As a consequence, improvements at each stage of the cascade of care should also be informed by a thorough understanding of the dynamics of care.

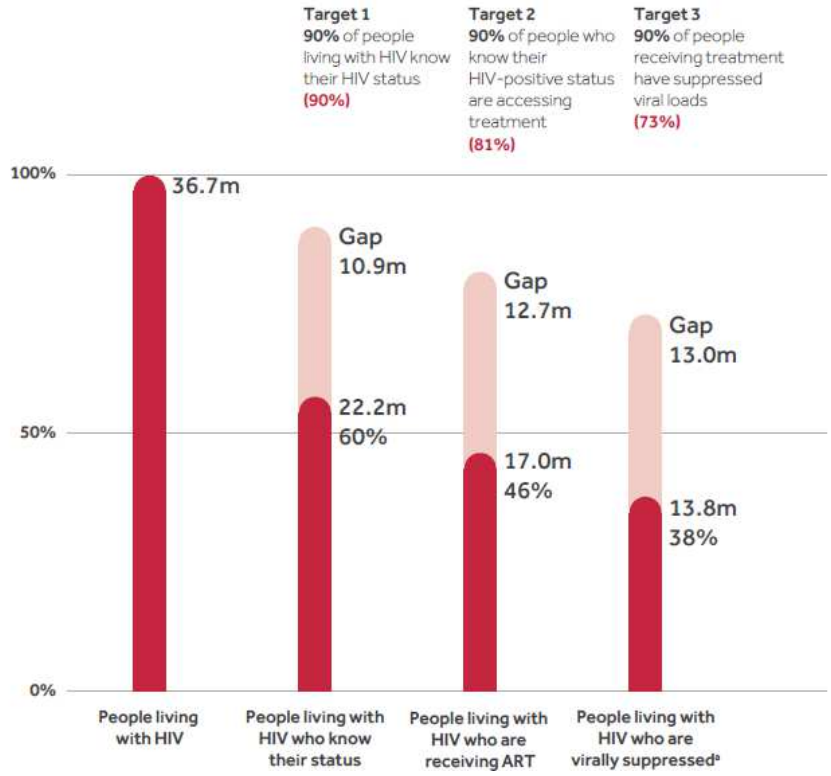


Figure 15: Gaps in the HIV care cascade in 2015 [68]

The measure of the number of people who know their HIV status was derived from data reported by 87 countries accounting for 79% of the people living with HIV globally. The measure for the number of people with suppressed viral loads was derived from data reported by 86 countries. Globally, 22% of all people receiving ART were reported to have received a viral load test. [a] HIV-1 RNA <1000 copies/ml

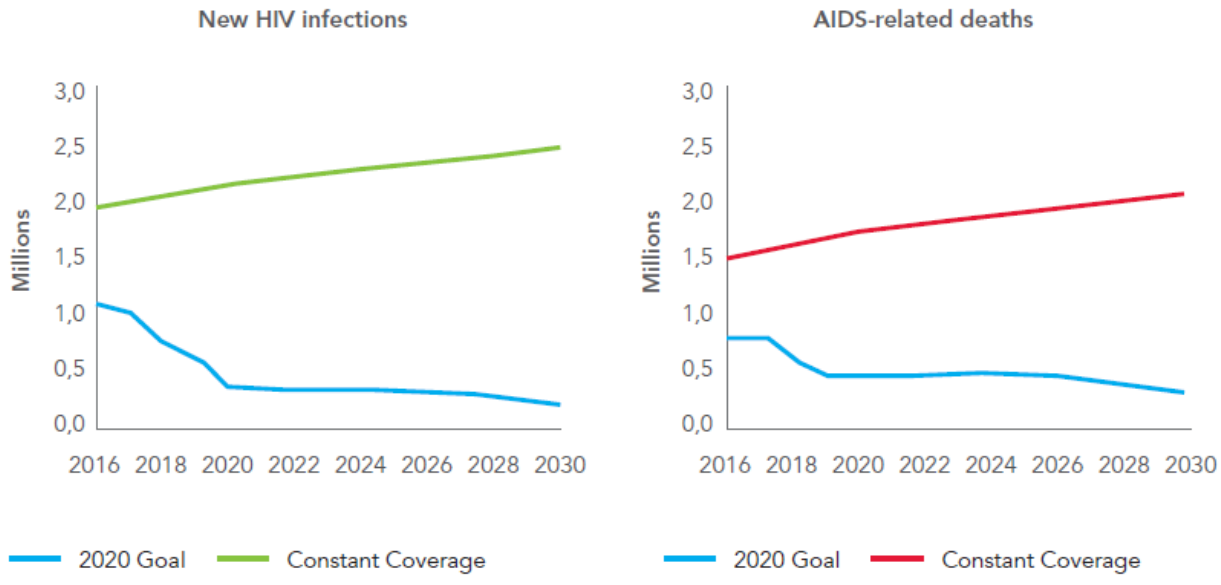


Figure 16: Impact of the 90-90-90 target on HIV infections and AIDS-related deaths, 2016-2030 [9]

1.3.1.2. Target 1: HIV testing

HIV testing and counselling is the first crucial step of the cascade of care. Individuals who are unaware of their positive HIV status will remain out of care with consequent increased morbidity and mortality and would be more likely to transmit the virus to sexual partners as they would not be on ART coupled with reported increased risk in sexual behaviour [164]. However, despite high HIV burden in sub-Saharan Africa, testing coverage is low, particularly among young adults and men. In 2013, an estimated 71% of women and 83% of men in sub-Saharan Africa had never been tested for HIV [165]

Research has shown that deterring uptake of HIV testing includes a low perception of risk, concerns about confidentiality and fear of disclosure, stigma and discrimination , all factors that have been suggested as explanations for the low testing rates in sub-Saharan Africa. Gender inequity that leaves women economically dependent on men may undermine the ability of women to seek HIV testing [166, 167]. Several strategies have proven successful to increase the number of people who know their HIV positive status, including the use of community opinion leaders, home-based family delivered counselling and testing, provider-initiated counselling and testing, and community-level counselling and testing. Additionally, assistance with disclosure and partner testing, or the advancement of counselling and testing for couples can help identify partners who are infected and in need of treatment or who are not infected and in need of protection [168].

1.3.1.3. Target 2: Linkage to care and ART initiation

Failure to initiate timely HIV care after diagnosis is common. Longer delays in linkage with medical care are associated with greater likelihood of progression to AIDS by CD4 cell criteria. Similar to individuals with undiagnosed infections, HIV-infected individuals not engaged in care pose a greater risk of ongoing HIV transmission [169]. In 2012, in sub-Saharan Africa, it was estimated that only 57% of those diagnosed HIV-positive have linked to care [170]. The majority of them started ART within one month.

Barriers to linkage to care include transport costs, distance to clinics, concerns about disclosure and stigma, staff shortages, long clinic waiting times, male gender and younger age [171]. Several approaches have been taken to reduce losses between HIV testing and entry into care, including health system interventions (e.g. integration in the setting of antenatal care); patient convenience and accessibility (e.g. point-of-care CD4 count testing with immediate results, home-based ART initiation); behaviour interventions and peer support (e.g. improved communication, patient referral and education) and incentives (i.e. food support) [172].

1.3.1.4. Target 3: Viral suppression

HIV-positive individuals who enter into medical care and initiate ART are encouraged to retain in care and adhere on ART, meaning continuously engage with the healthcare system and comply with their prescribed treatment regimen. A poor engagement in care is associated with poor health outcomes including an increased risk of developing opportunistic infections, an increased risk of viral resistance for those who take ART intermittently, and an increased risk of mortality [173]. Additionally, individuals who are not on ART contribute to ongoing HIV

transmission in the community. As ART coverage increases worldwide, modelling studies suggest that people currently or previously on ART are likely to play an increasingly large role in HIV transmission. Indeed, while ART greatly reduces transmission risk, transmission has been observed to occur from people receiving ART, albeit at an extremely low rate [174], and it is plausible that the rate of transmission will be higher among people not part of research cohorts [175]. A systematic review in sub-Saharan Africa showed that the proportion of patients retained in pre-ART care was 45% when CD4 eligibility threshold was 200 cells/mm^3 [170]. Another systematic review in sub-Saharan Africa showed that viral suppression (Viral load <50 copies/mL) among individuals eligible for treatment after 12 months of ART was 76% [176].

A meta-analysis involving 37 qualitative and 47 quantitative studies on barriers and facilitators to adherence identified fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, complex ART regimens, high pill burden, decreased quality of life, work and family responsibilities, falling asleep and access to medications as the main adherence barriers [177]. Interventions that improved both adherence and clinical outcomes have been shown to address the patients' beliefs as well as other practical issues that facilitate or hinder their ability to adhere. Examples include adherence counselling, a once-daily regimen (compared to twice daily), text messaging, web-based cognitive behavioral intervention; face-to-face multi-session intensive behavioral interventions, and nurse-delivered home visits combined with telephone calls [178]. As individuals do not adhere to ART, they contribute to ongoing HIV transmission in the community.

1.3.2. The HIV care cascade in South Africa

In South Africa, a national study was conducted in 2012 to characterize engagement within HIV care [179]. It is estimated that less than one third of adult males over the age of 15 have ever tested for HIV. Among 6,4 million people living with HIV, an estimated 3,3 million persons (52%) accessed care and 34% were on ART. While viral suppression rate was 73% among the treated population, the overall percentage of persons with viral suppression among the HIV-infected population was 25%, corresponding to potentially 4,5 million infectious persons (Figure 17). Males and the sexually active 15-49 year age-group had poorer engagement in all stages of care [170].

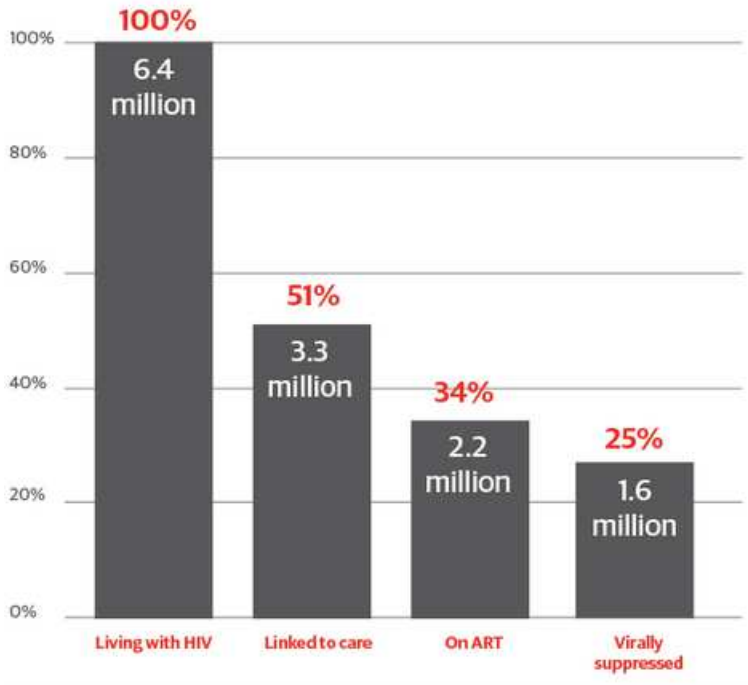


Figure 17: Engagement in care in South Africa, 2012 (adapted from [179])

In 2014 and 2015, a cross-sectional survey was conducted in a high-burden district of the KwaZulu-Natal province in South Africa, close to the TasP trial study area, to assess the 90-90-90 targets achievements [180]. It was estimated that none of the targets: among the 9,812 participants enrolled, 60% knew their HIV-positive status, and 70% of them were on ART (Figure 18). While viral suppression rate was 88% among the treated population, the overall percentage of persons with viral suppression among the HIV-infected population was 53%.

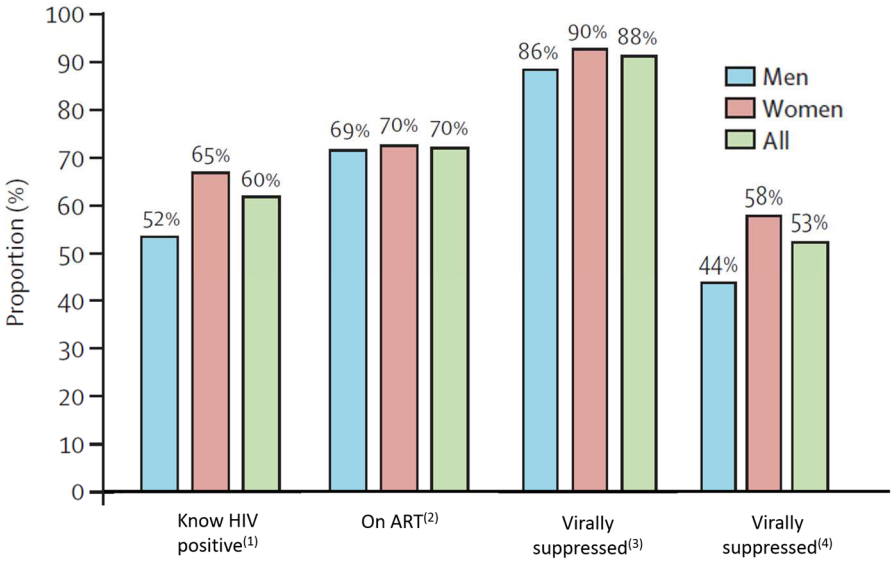


Figure 18: Engagement in care in a cross-sectional survey conducted in uMgungundlovu district, KwaZulu-Natal, South Africa, 2014-2015 (n=9,812) [180]

Percentages are based on the number of HIV-positive people and are population weighted. ART=antiretroviral therapy. (1)Among participants who tested HIV-positive, (2)Among participants who knew that they were HIV-positive, (3)Among participants who were on ART, (4)Among all HIV-positive participants, irrespective of ART status.

CHAPTER II
PhD FRAMEWORK

In this chapter, we describe the problem from which this PhD research stems, the main objective as well as the geographical, institutional and programmatic settings in which my research was embedded.

2 PhD FRAMEWORK

2.1. Problem

For now, the hypothesis that UTT strategies have a significant impact on the HIV epidemic at the level of a whole community is based on mathematical modelling estimations. To achieve the full potential impact of UTT, it requires the large-scale implementation of health interventions that participate in maximizing the coverage of HIV testing, effective linkage and retention in care, rapid access to and initiation of ART, and strong adherence for viral suppression. Given the unprecedented HIV services uptake rates required, pressing research questions need to be answered on the feasibility, acceptability, cost-effectiveness and sustainability of the UTT interventions [2]. Such evidence would be key to guide future policy planning and practice, by providing evidence for optimal wide scale implementation of UTT strategies in the routine health system.

My doctorate offers to answer some of those questions. I focused my work on three gaps of the scientific literature, using the TasP trial as an example:

- First, as there is neither “UTT gold standard” per say, nor “all-inclusive package of UTT interventions”, it is unclear how the UTT concept has been understood, defined and implemented in various contexts.
- It is also unknown how HCWs exposed to UTT understand and claim ownership over UTT strategies.
- Finally, it is also unknown how individuals exposed to UTT react to the integration of those innovative interventions in their care routine.

2.2. Objectives

2.2.1. General objective

To provide an understanding of the implementation of UTT in sub-Saharan Africa, with the example of the ANRS 12249 TasP (TasP) trial in South Africa.

2.2.2. Specific objectives

- Specific objective 1: To characterize and compare the UTT approaches of the five UTT population-level randomized trials in sub-Saharan Africa including the TasP trial
- Specific Objective 2: To describe the experiences and perceptions of HCWs on the feasibility and acceptability of the UTT strategy developed and used in the TasP trial
- Specific Objective 3: To analyse the care pathways of people living with HIV within the UTT care of cascade of the TasP trial
-

2.3. PhD setting

2.3.1. Institutional setting

2.3.1.1. Infectious diseases in lower-income countries research team – Bordeaux Population Health

My PhD was conducted within the French research team named “Infectious diseases in lower-income countries” (IDLIC), part of the Bordeaux Population Health research centre Inserm U1219 (http://www.bordeaux-population-health.center/en/teams/infectious-diseases-in-lower-income-countries-idlic/). The team is currently directed by Dr Xavier Anglaret. The research team focuses on a variety of diseases in various geographic locations with an important focus on HIV/AIDS in Africa. It has a strong relationship with Ivory Coast through the international epidemiological database to evaluate AIDS (IeDEA) in West Africa (US NIH) and the French ANRS clinical trial unit for lower-income countries (MEREVA). It also has a strong partnership with South Africa thanks to the Africa Health Research Institute (AHRI).

Both of my PhD directors develop their research within the IDLIC team. Joanna Orne-Gliemann is a public health, research scientists, co-supervisor of the “International Health” Master degree at the Bordeaux School of Public Health (ISPED). She co-coordinated the TasP trial. Her research interest encompasses human sciences and social epidemiology on themes such as HIV/AIDS prevention and care, multi-morbidity, mother and child health, sexual and reproductive health, gender and social relationships. François Dabis is a Professor of Epidemiology at the Bordeaux School of Public Health. He is the former IDLIC director and current director of the French National Agency for AIDS and Viral Hepatitis Research (ANRS). He was the co-principal investigator of the TasP trial. His research interests notably encompass the public health challenges of HIV prevention and care (prevention of mother-to-child transmission in Africa, prognosis of antiretroviral-treated adults and children in France and West Africa and more generally operational research on HIV programs and their outcomes, universal test and treat in South Africa).

2.3.1.2. Africa Health Research Institute

The PhD research was embedded in the research agenda of the Africa Health Research Institute (AHRI) (formerly Africa Centre for Population Health) (https://www.ahri.org/). AHRI is a Wellcome Trust-funded research institution affiliated to the University of KwaZulu-Natal. The director is Pr Deenan Pillay. It carries out population-based demographic and health surveys in an area of the sub-district known as the Population Intervention Platform Study Area (PIPSA) which measures 825 km^2 with a mid-year population of 151,441 in 2015 (Figure 21). The PIPSA was implemented in January 2017 as a newly expanded research platform combining the former AHRI HIV surveillance area [181] and the TasP trial area.

2.3.2. PhD research field

My PhD work was conducted in Hlabisa health sub-district, uMkhanyakude district, in northern KwaZulu-Natal province, South Africa, and embedded in the research agenda of the AHRI research institute (Figure 19). Hlabisa health sub-district is an area of 1,430 km^2 with a population of approximately 248,000 [20]. The majority of the community lives in scattered homesteads that are not concentrated into villages or compounds (Figure 20). It is one of the most deprived areas in South Africa, with 43% unemployment and only 37% of the population having access to piped water inside dwellings [20].

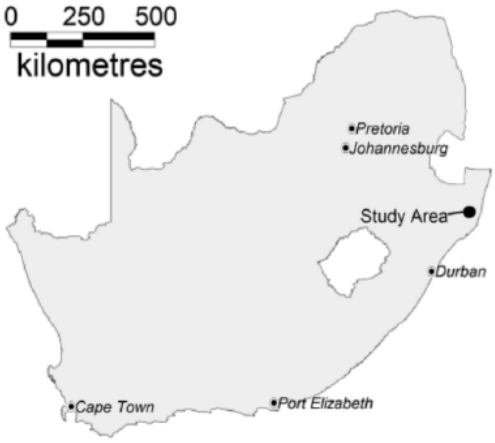


Figure 19: Map showing location of Hlabisa sub-district within South Africa



Figure 20: Hlabisa sub-district (Photo credit: Africa Health Research Institute)

Hlabisa health sub-district is a prime example of a rural district with a huge burden of morbidity and mortality attributable to HIV [21]. The crude HIV incidence in the AHRI HIV surveillance area in the period 2004-2011 was estimated at 2.63 new infections per 100 person-years (95% CI 2.50-2.77) in people 15 years and older [22]. Estimated HIV prevalence was 29% in 2011 for those aged 15-49 years [23]. One of the major features of the current local health system is the decentralization of primary health care [24]. There are currently 17 local clinics in the area (Figure 21). Nurses are in charge of the clinic management, including the ART programme (national program for Nurse-initiated management of ART [NIMART]). A medical doctor from the unique sub-district local hospital is expected to visit each clinic once a month. Besides, a network of community members exists in a few areas of the sub-district to visit people's home and provide basic health services such as counselling for linkage to HIV care. They are referred to as community care givers (CCGs). At the time of initiation of my research, the ART coverage within the demographic/HIV surveillance area was 37% of all HIV-infected individuals [22].

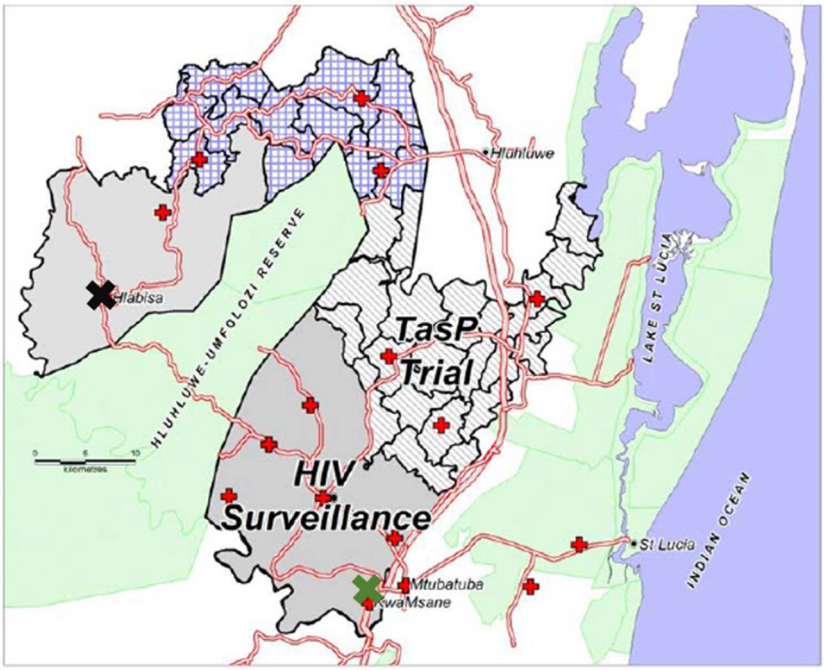


Figure 21: Map of Hlabisa sub-district showing location of the primary health care clinics
The black cross indicates the Hlabisa district hospital. The green cross indicates the Africa Health Research Institute (AHRI). The red crosses indicate primary health care clinics. The grey shaded area represents the HIV surveillance area of the AHRI. The stripped area represents the ANRS 12249 TasP trial area.

2.3.3. TasP trial

The rationale of the TasP trial was based on the model developed by Granich and colleagues in 2009 [11]: “Testing of all individuals of a community, followed by initiation of ART of all individuals diagnosed HIV positive will lead to the end of the epidemic in the next 10 to 30 years”. The TasP trial was a two-arm cluster randomized trial implemented between March 2012 and June 2016 in 22 clusters (2 x11) to investigate the impact of population ART on HIV incidence (Figure 22) [19]. The TasP trial was conducted in communities outside of the former AHRI HIV surveillance area on the northern side, as illustrated in Figure 21.

The trial had two main components (Figure 23): the first was a population-based home survey comprising the offer of six-monthly home HIV testing using rapid test technology and the referral of those identified HIV-positive to the trial clinic in their cluster (Figure 24) while the second was related to the clinical care of HIV-positive individuals who linked to the trial clinics following referral (Figure 25). At the time of referral, HIV-positive individuals were either newly diagnosed or already knew (and reported) their status to be HIV-positive. Some of the latter individuals were receiving ART from the Hlabisa public ART programme (Figure 26). ART-naïve HIV-positive adults in the intervention arm were offered immediate ART initiation upon enrolment in trial clinics. The HIV-positive adults in the control arm were offered ART according to the prevailing national guidelines (CD4 $\leq$350 cells/mm^3, WHO stage 3 or 4 disease or drug-resistant TB) [25]. In January 2015, following revised WHO guidelines, the new South African national department guidelines recommending initiation of ART at a CD4 $\leq$500 cells/mm^3 was adopted in the control arm of the trial [26]. Additionally, from May 2013, phone and home-based support for linkage to trial clinics was offered to individuals not linked to care within three months after referral (Figure 27).

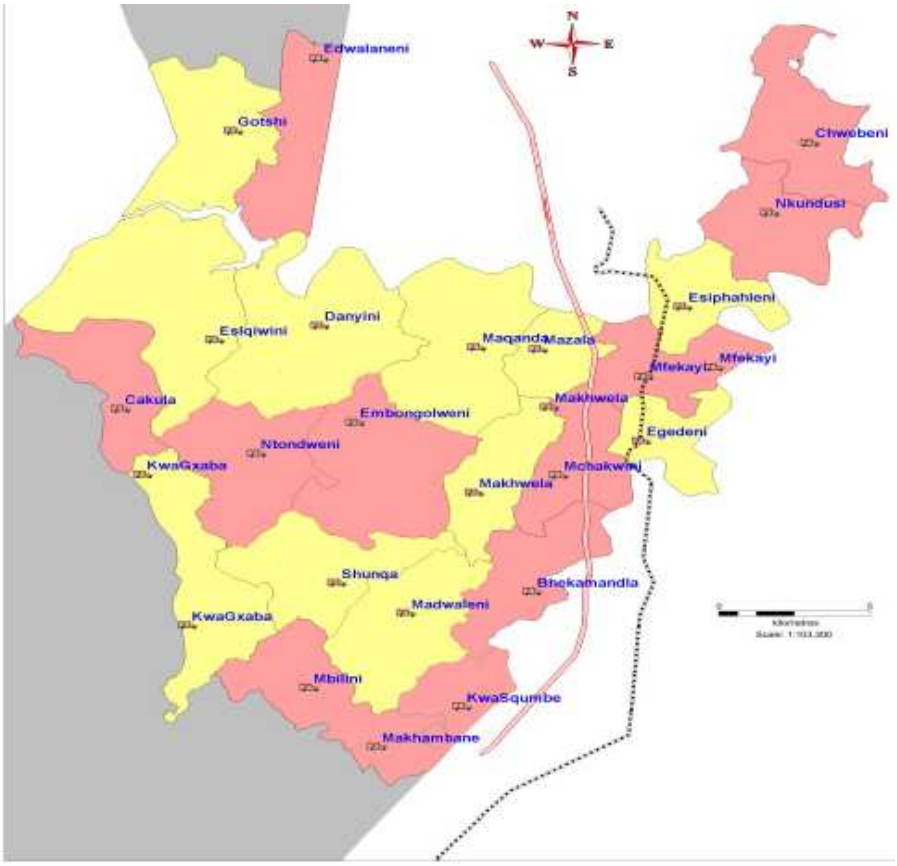


Figure 22: Map of the ANRS 12249 TasP trial clusters showing the location of the trial specific clinics

The TasP trial clinics are represented with vehicles icons. Pink and yellow areas respectively represent control and intervention clusters.

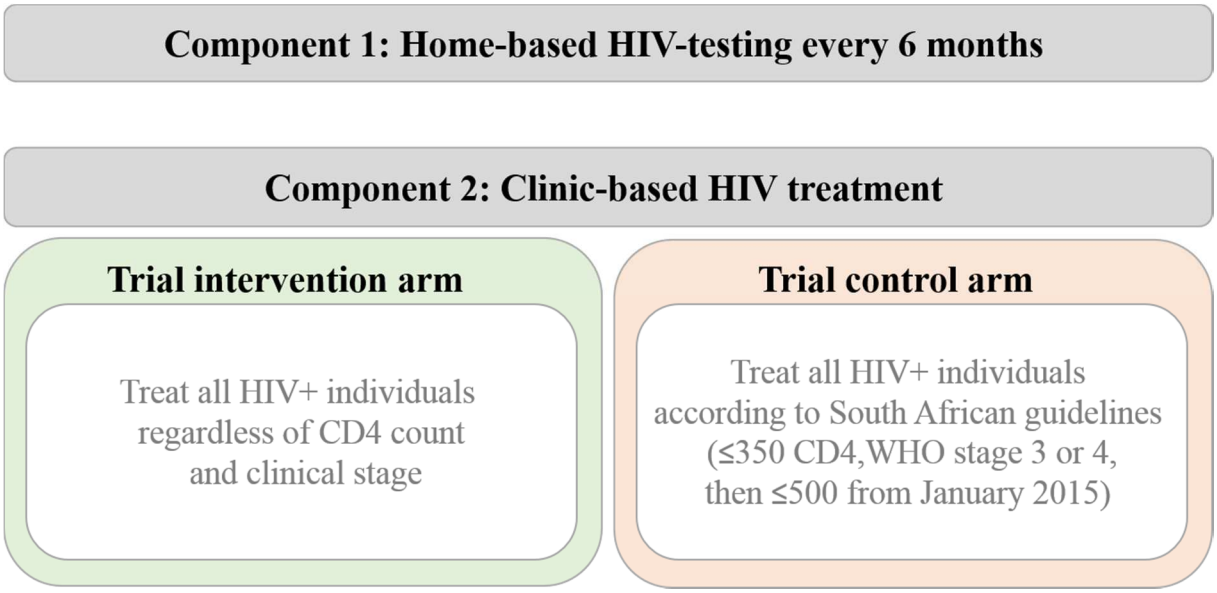


Figure 23: Description of the main components of the ANRS 12249 TasP trial (March 2013 – June 2016) [19]



Figure 24: These health care workers offer HIV testing to a participant to the ANRS 12249 TasP trial at her home (Photo credit: Africa Health Research Institute)



Figure 25: Trial clinic of the ANRS 12249 TasP trial (Photo credit: Africa Health Research Institute)



Figure 26: Government clinic of the Hlabisa health sub-district (Photo credit: Africa Health Research Institute)



Figure 27: These health care workers visit homes of people who did not link to care or didn't retain in care in the ANRS 12249 TasP trial to offer them support (Photo credit : Africa Health Research Institute)

CHAPTER III
RESULTS

The following chapter presents the background, methods and results of the PhD original research. It is articulated in three parts: (i) state of the UTT research in sub-Saharan Africa, (ii) views of health care workers regarding UTT, (iii) care trajectories of people living with HIV in a UTT strategy. For each of them, manuscripts have been published, are under revision or are being prepared. Some of these original work have also been presented in national and international conferences.

3 RESULTS

3.1. State of the UTT research in sub-Saharan Africa

The key findings of this study are currently in the final stages of revision of a manuscript prior to publication in the Journal of the International AIDS Society. The submitted manuscript is entitled “Comparative assessment of five trials of universal HIV testing and treatment in Sub-Saharan Africa”. It is included at the end of this section.

3.1.1. Background

The evidence of the impact of ART on reducing HIV transmission at the individual level [7] brought researchers to put forward the hypothesis that ART could help contain the epidemic by reducing contamination risk for non-infected persons at population-level. Mathematical models suggest that universal and repeated HIV testing, and immediate treatment for all HIV-positive persons (Universal Test and Treat strategy, [UTT]) could overcome the HIV epidemic in 30 years in such countries as South Africa [10, 11, 13]. Several randomized controlled trials (RCTs) have been launched in the previous five years to provide empirical evidence for optimal wide scale implementation of UTT interventions in whole communities [182]. They are conducted in countries with some of the world's highest HIV prevalence rates: PopART in South Africa and Zambia, TasP ANRS 12249 in South Africa, BCPP in Botswana, SEARCH in Kenya and Uganda and MaxART in SwaZiland (Figure 28). As there is yet no « UTT gold standard » per say, their results will be key to guide future policy planning and practice of UTT in the context of the day-to-day realities faced by health systems and communities. In order to facilitate joint analyses that can inform public policy and resource allocation, the investigators of those studies agreed to collaborate as the Universal Test and Treat Trials Consortium (UT^3C).

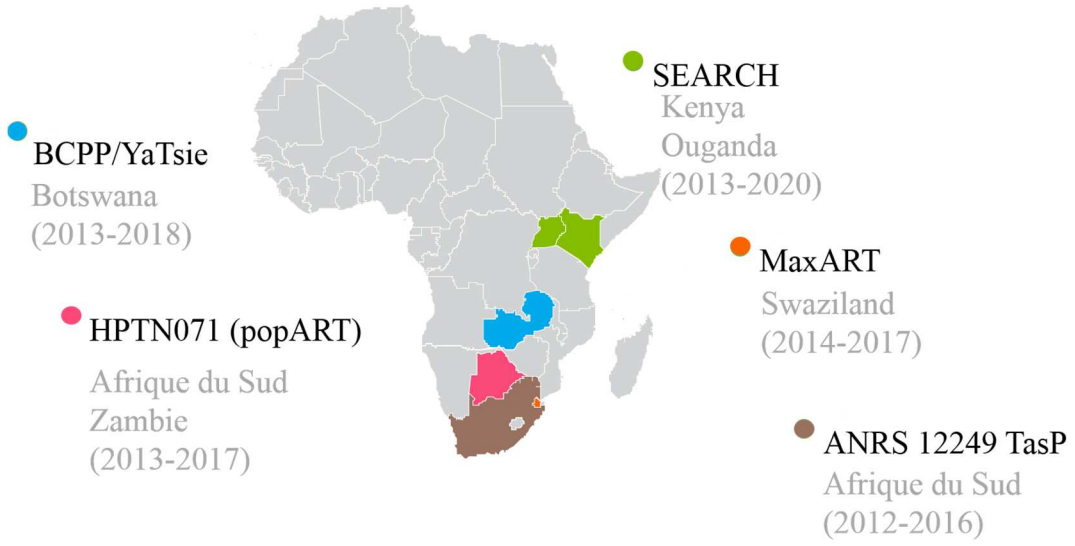


Figure 28: Map of the countries of implementation of the five Universal-Test-and-Treat studies in sub-Saharan Africa

3.1.2. Objective

The main objective of this work was to describe, compare and contrast the contexts, research designs, intervention packages, themes explored and adaptations, that characterize the five ongoing large-scale studies on UTT in Southern and Eastern Africa.

3.1.3. Methods

We conducted a comparative assessment of the five trials using data extracted from study protocols and collected during baseline studies, with additional input from study investigators. We organized differences and commonalities across the trials in five categories: trial contexts, research designs, intervention packages, trial themes and adaptations (Figure 29).

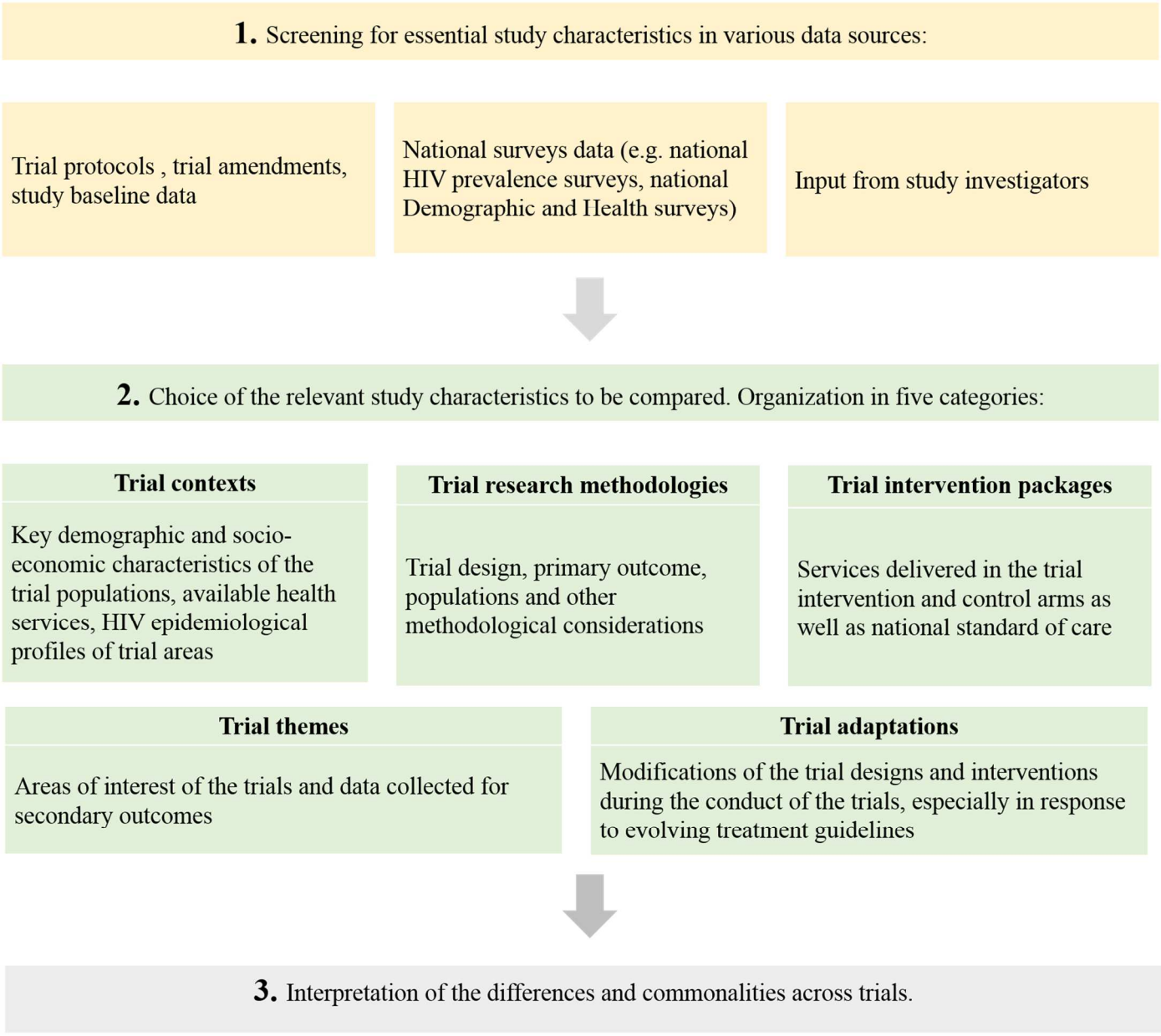


Figure 29: Methodological details of the comparative assessment of the five ongoing large-scale studies on UTT in Southern and Eastern Africa.

3.1.4. Principal results and discussion

All five studies were conducted in a diversity of social, demographic, economic, political and health systems settings. As part of their UTT strategies, they all offered immediate ART initiation to trial participants, almost systematically including community-based HIV testing and more rarely including other biomedical interventions such as voluntary medical male circumcision. By highlighting the extent of those disparities across trials as well as the specificities of study designs, our analysis provides policy-makers and program planners with a comprehensive overview of the trial characteristics, which are likely to affects the results of the implemented UTT strategies and challenge future comparisons of trial findings. For now, only the TasP trial yielded final results. It did not demonstrate an effect of offering immediate ART on HIV incidence [183]. In this rural South African study setting, such result highlights linkage to care as the main bottleneck to UTT implementation. As it happens, the SEARCH trial, still ongoing, recently reported having nearly doubled HIV viral suppression within their study population over two years (from 44.7% to 80.2%), surpassing the UNAIDS 90-90-90 targets [184]. As we discuss in the paper, the pragmatic systems and processes of UTT care models that are being field-tested in the trials are on the forefront of large-scale practice. Only a careful analysis of the evidence of their impact on the HIV epidemic will allow to efficiently prepare health systems and communities to maximize their impact in countries with some of the world's highest prevalence rates.

3.1.5. Role of the PhD candidate

Together with my PhD directors, I participated in initiating the UT^{3}C consortium in January 2015. I wrote the proposal for this first collaborative work that I was designated to lead. In the following year and a half, I coordinated the gathering of trial information via emails (twice monthly). Then, pairing with my PhD director François Dabis, I led monthly teleconferences as well as a half-day meeting prior to the manuscript submission.

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REVIEW

Comparative assessment of five trials of universal HIV testing and treatment in sub-Saharan Africa

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Trial registrations

**The Universal Test and Treat Trial Consortium (UT^{3}C) is composed of the teams of five ongoing trials: the BCPP trial (ClinicalTrials.gov NCT01965470, https://clinicaltrials.gov/ct2/show/NCT01965470), the *Max*ART trial (ClinicalTrials.gov NCT02909218, https://clinicaltrials.gov/ct2/show/NCT02909218), the HPNT071 trial (PopART trial) (ClinicalTrials.gov NCT01900977, https://clinicaltrials.gov/ct2/show/NCT01900977), the SEARCH trial (ClinicalTrials.gov NCT01864603, https://clinicaltrials.gov /ct2/show/NCT01864603) and the ANRS 12249 TasP trial (ClinicalTrials.gov NCT01509508, https://clinicaltrials.gov /ct2/show/NCT01509508).

Abstract

Design: Universal voluntary HIV counselling and testing followed by prompt initiation of antiretroviral therapy (ART) for all those diagnosed HIV-infected (universal test and treat, UTT) is now a global health standard. However, its population-level impact, feasibility and cost remain unknown. Five community-based trials have been implemented in sub-Saharan Africa to measure the effects of various UTT strategies at population level: BCPP/YaTsie in Botswana, *Max*ART in Swaziland, HPTN 071 (PopART) in South Africa and Zambia, SEARCH in Uganda and Kenya and ANRS 12249 TasP in South Africa. This report describes and contrasts the contexts, research methodologies, intervention packages, themes explored, evolution of study designs and interventions related to each of these five UTT trials.

Methods: We conducted a comparative assessment of the five trials using data extracted from study protocols and collected during baseline studies, with additional input from study investigators. We organized differences and commonalities across the trials in five categories: trial contexts, research designs, intervention packages, trial themes and adaptations.

Results: All performed in the context of generalized HIV epidemics, the trials highly differ in their social, demographic, economic, political and health systems settings. They share the common aim of assessing the impact of UTT on the HIV epidemic but differ in methodological aspects such as study design and eligibility criteria for trial populations. In addition to universal ART initiation, the trials deliver a wide range of biomedical, behavioural and structural interventions as part of their UTT strategies. The five studies explore common issues, including the uptake rates of the trial services and individual health outcomes. All trials have adapted since their initiation to the evolving political, economic and public health contexts, including adopting the successive national recommendations for ART initiation.

Conclusions: We found substantial commonalities but also differences between the five UTT trials in their design, conduct and multidisciplinary outputs. As empirical literature on how UTT may improve efficiency and quality of HIV care at population level is still scarce, this article provides a foundation for more collaborative research on UTT and supports evidence-based decision making for HIV care in country and internationally.

Keywords: HIV; universal test and treat; randomized trials; comparative assessment; protocols; sub-Saharan Africa

Additional Supporting Information may be found online in the Supporting information tab for this article.

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1 | INTRODUCTION

In recent years, the debate regarding "treatment versus prevention" for HIV infection has shifted with adoption of the concept of "treatment-as-prevention" (TasP). Together with other compelling evidence from observational, ecological and modelling studies [1-5], the landmark HIV Prevention Trial Network (HPTN) 052 trial showcased TasP as a promising means to curb the global HIV epidemic. Indeed, the use of antiretroviral therapy (ART) was shown to be associated with

a 93% reduction in HIV sexual transmission in HIV serodiscordant stable couples in whom the HIV-positive partner was randomized to immediate initiation of ART irrespective of his/her individual clinical needs [6]. Since then, the scientific rationale for TasP has expanded. In 2015, two randomized clinical trials showed that initiating ART as soon as possible after HIV diagnosis (regardless of disease stage) also yielded strong clinical benefits to the individual [7,8].

The concept of TasP has been replaced by that of universal HIV testing and treatment (UTT), which offers HIV counselling and testing to an entire population and ART to all those HIV-infected [9]. In 2015, the World Health Organization (WHO) recommended that ART should be offered to all individuals diagnosed with HIV regardless of their CD4 count and clinical staging [10], and the Joint United Nations programme on HIV/AIDS (UNAIDS) proposed their 90-90-90 targets for HIV treatment scale-up by 2020 (namely, that 90% of HIV-infected persons know their status; that 90% of those who know their positive HIV status continue on an efficacious ART regimen; and that 90% of those on ART have undetectable HIV-1 RNA) [11]. Thus, the remaining research questions are "What are the feasibility, effects and costs of UTT on a population level, and how do we best implement this strategy?" Maximizing the coverage of HIV testing, effective linkage and retention in care, rapid access to and initiation of ART, and strong adherence for viral suppression are required to achieve the full potential impact of UTT [12-14], both on individual health outcomes for people living with HIV and on HIV incidence reduction.

Mathematical models have sought to predict the long-term population-level impact of UTT strategies on the epidemic [15,16]. All models have indicated that UTT could reduce HIV-transmission, but the estimated impact of the UTT strategy on the reduction of HIV incidence ranged from 35% to 54% in the short-term and from 32% to 74% in the longer term [16]. Furthermore, these models vary greatly in structure and in parametric assumptions and rely on context-specific variables, such as eligibility criteria for ART initiation, uptake and coverage of HIV testing, linkage to care, treatment initiation and adherence [13]. Modelling the potential impact of UTT offered necessary but insufficient data points for national policy makers trying to determine how to successfully take UTT to scale in their unique contexts. As noted by the HIV Modelling Consortium, modelling is used to investigate the *potential* impact of UTT; empirical evidence from large randomized trials is needed to further assess the feasibility of rolling out UTT to whole communities [17].

As such, in a context where HIV funding is flat, obtaining evidence-based data on UTT long-term impact, cost-effectiveness, feasibility, sustainability and acceptability at local and national levels is critical [15,18]. To fulfil this need, five community-based trials were designed and implemented in the past five years in Southern and Eastern Africa. They were initiated before the WHO issued its recommendation for universal treatment [19], i.e. in a period of more restricted ART use [20]. The common aim of these trials was to evaluate the effectiveness of UTT on HIV control in some of the most affected populations in sub-Saharan Africa [21-25]. In addition to measuring effects of UTT on HIV incidence, the studies are expected to provide critical data on the feasibility and cost of implementation of UTT (as well as more vs. less successful approaches to implementation), and thus to guide future policy and practice, by providing evidence for optimal scale-up approaches [12].

Although the data collection of four out of five trials is not completed yet, the ongoing UTT trials have accumulated practical experience and data which could prove vital to large-scale rollout of UTT strategies. The investigators of the five ongoing UTT randomized population-based studies have agreed to collaborate as the Universal Test and Treat Trials Consortium (UT^3C). This group shares protocols, field experiences and early data, to generate consensus statements when appropriate, and ultimately to facilitate joint analyses that can inform public policy and resource allocation.

The aim of this first paper is to describe, compare and contrast the contexts, research designs, intervention packages, themes explored and adaptations, that characterize these five ongoing large-scale studies on UTT in Southern and Eastern Africa. This comparison will facilitate a better understanding of the results of these studies, when they are available, and may assist in understanding any differences found.

2 | METHODS

2.1 | Design

We conducted a comparative assessment of the five large-scale UTT randomized studies conducted in sub-Saharan Africa: the ANRS 12,249 TasP (ANRS TasP) trial in South Africa [21], the *Max*ART study in Swaziland [22], the HPTN 071 (PopART) trial in South Africa and Zambia [23], the SEARCH trial in Uganda and Kenya [24] and the BCPP/YaTsie (BCPP) trial in Botswana [25]. UTT trials gathered as a consortium (UT^3C) constituted of two to three representatives per trial, including a trial principal investigator. After sharing trial protocols, we screened for essential study characteristics and consensually decided which should be compared and at what level of detail. Then we highlighted and interpreted differences and commonalities across the trials. Over a year and a half period, information was exchanged via emails (twice monthly), teleconferences (once monthly) and a half-day meeting held prior to the manuscript submission. The first and last authors of the present manuscript led this collaborative work.

2.2 | Sources of information

We first extracted information from the trial protocols: BCPP V4.0 (7 December 2015 for Evaluation Protocol, and 15 April 2016 for Intervention Protocol) [26], *Max*ART V2.0 (7 September 2015) [22], PopART V3.0 (16 November 2015) [23], SEARCH V7.0 (5 February 2016) [27], ANRS TasP V3.0 (12 March 2015) [21]. We also extracted data from amendments to the trial protocols and sought input (including confirmation of accuracy) from study investigators where necessary. Finally, we included data from the study baseline and from national surveys (e.g. national HIV prevalence surveys, national Demographic and Health surveys, national Population and Housing censuses, national Poverty surveys, national Labour surveys, national UNAIDS global AIDS response reports, statistics of the United Nations Educational, Scientific and Cultural Organization, WHO country statistical profiles, World Bank reports).

2.3 | Analysis

We identified study characteristics that were deemed essential for comparing the UTT trials and organized them in five categories: (1) Trial contexts: key demographic and socio-economic characteristics of the populations living in the trial areas, health services available in the trial areas, and their HIV epidemiological profiles; (2) Trial research methodologies: trial design, primary outcome, populations and other methodological considerations; (3) Trial intervention packages: services delivered in the trial intervention and control arms as well as national standard of care; (4) Trial themes: areas of interest of the trials and data collected for secondary outcomes; (5) Trial adaptations: modifications of the trial designs and interventions during the conduct of the trials, especially in response to evolving treatment guidelines. The identification of those five categories as well as the interpretation of the results was done collectively, until a consensus was reached within the cross-study collaboration.

3 | RESULTS

3.1 | Trial contexts

Table 1 characterizes the trial population and their contexts at baseline (See Table S1 for national indicators). The trials vary in terms of the demographic composition. For example in SEARCH, half of the population living in the trial area is less than 15 years old (unpublished trial data), whereas in the South African study sites of PopART,26% of people are aged ≤15 years old (unpublished trial data). The trial contexts also differ in the economies involved (e.g. unemployment, poverty) as well as the education level of their populations. The proportion of adults who had no secondary school education ranged from 13% in the South African communities of PopART (unpublished data) to 71% in the SEARCH communities [28]. While all trials are conducted in areas which suffer from generalized HIV epidemics, the baseline prevalence of HIV also varied and was estimated to be 30% TasP trial sites [29], 29% in BCPP [30], 29% in *Max*ART [31], 22% in the South African sites of the PopART (unpublished data), 21% in the Zambian sites of PopART (unpublished data), 20% in SEARCH Kenyan communities [32], and is less than 10% in the SEARCH Ugandan communities [32]. Finally, important disparities are observed across trials in relation to the extent of development of the HIV health systems at baseline. The *Max*ART and BCPP trials are being implemented in areas characterized by a relatively high ART coverage with, respectively, 85% [33] and 73% [30] of the adult population over 15 years old on ART. In SEARCH, an estimated 57% of people ≥15 years old are on ART at baseline [32]. TasP and PopART trials accounted for the smallest ART coverages with less than half of the population on ART in their study sites (38% among >15 years old in TasP [34], 30% and 39% among 18 to 44 years old in the South African and Zambian PopART communities (unpublished work)). Despite significant progress of the local governments in fighting the epidemics through a series of strategic and operational plans, the overall health sector response and capacity have not yet met the needs of the local population in all these settings. The epidemics continue to spread along socio-economic development fault lines such as poverty, gender inequality, unemployment and lack of adequate social protection among others [35].

3.2 | Trial research designs

As presented in Table 2, the five UTT trials share a common primary aim, which is to assess the impact of UTT on the HIV epidemic. Each trial compares outcomes between communities where all HIV-infected persons are offered ART regardless of immunological status or clinical stage (among other interventions) and communities where HIV-infected persons receive ART according to the national guidelines. All trials examine the long-term benefits and sustainability of the UTT intervention with their extended observation periods (≥3 years). With this common framework, the trials differ somewhat in their designs, with four adopting a community-randomized design and one adopting a stepped-wedge clinic-randomized design. The trials also differ in the number of study arms, with four trials designed with two arms and one trial with three arms.

With study-specific definitions of residency, Table 3 shows that the selection of the trial clusters (i.e. communities or clinic-catchment areas) were based on diverse criteria. All trials made efforts for their clusters to be large (to ensure that most sexual contacts occur within the cluster) and dispersed (to minimize contamination and overlapping catchment of different health facilities). Two out of the five trials are implementing a pair-matched design, and one trial is triplet-matched. With study-specific definitions of residency, the trial population and eligibility criteria and sizes varied greatly between studies. All trials carefully defined the population that was eligible for the trial interventions (intervention population) which ranged from 4000 to a million of individuals. They collect specific information on selected samples (research study population) and measure the primary outcome through more intensive observations (evaluation population). The study settings are all characterized by some degrees of mobility in and out of the study communities. (Migration rates and characteristics of migrants will be reported in trial-specific publications.)

3.3 | Trial intervention packages

As displayed in Table 4, the administration of universal ART is randomized at the community or clinic-level in all trials. Participants in the intervention arms are offered ART initiation regardless of immunological status or clinical stage. Initially BCPP participants were offered ART if CD4 count ≥350 cells/μl and HIV-1 RNA ≥10,000 copies/ml, or if CD4 count <350 cells/μl regardless of HIV-1 RNA. However, with emerging data and evolving WHO recommendations, all HIV-infected participants are now offered ART. In the control arms of all trials, ART initiation follows national guidelines. In the intervention arms of some trials, additional services are provided, enhanced and/or delivered according to the principles of differentiated care [48-51]: activities to engage the community in accessing HIV care (e.g. roadshows), intensive HIV voluntary testing options (e.g. mobile testing, home-based testing), intensified health prevention services (e.g. voluntary medical male circumcision (VMMC), screening for HIV-related diseases and non-communicable diseases), and support activities for linking and staying in care (e.g. counselling, short message service clinic appointment reminders, follow-up phone

Table 1. Trial background characteristics at baseline

Trial indicators	BCPP	*Max*ART	PopART	SEARCH	ANRS TasP
Census and demographic					
Residency	Rural and peri-urban	Peri-urban and rural	Peri-urban	Rural	Rural
Young in population living in trial area (%)[b]	42% aged <16 or >64 years old[b] [36]	38% aged <15 years old[c] (2013) [37]	SA: 26% aged ≤15 years old[b] Z: 40% aged ≤15 years old[b]	50% aged <15 years old[b]	30% aged <15 years old[c] (2013) [38]
Median age of research study population (years)[a]	40 years old [IQR: 33 to 48][a]	33 years old [IQR: 24 to 45][a]	27 years old [IQR: 22 to 33][a]	29 years old [IQR: 20 to 43][a] [28]	32 years old [IQR: 22 to 52][a] [34]
Female in research study population (%)[a]	64%[a]	64%[a]	SA: 69%[a] Z: 72%[a]	53%[a] [28]	70%[a] [29]
Labour and poverty					
Unemployed working-age population (%)	59%[a]	42%[c] (2013) [39]	SA: 72%[a] Z: 77%[a]	5%[a] [28]	90%[a] [34]
Population living under the national poverty lines (%)	15%[c] (2010) [40]	63%[c] (2009) [41]	SA: 54%[c] (2010) [42] Z: 46%[c] (2010) [43]	U: 19%[c] (2012) [44] K: 46%[c] (2005) [45]	54% (2010)[c] [42]
Education and health					
Adult population with primary education or less (%)	31%[a]	31%[a]	SA: 13%[a] Z: 35%[a]	71%[a] [28]	41%[a] [34]
HIV prevalence (%)	29% among 16 to 64 years old[a] (2013) [30]	29% among >15 years old[c] (2015) [31]	SA: 22% among 18 to 44 years old[a] (2014) Z: 21% among 18 to 44 years old[a] (2014)	SW-U: 7% among ≥15 years old[a] (2013) [32] E-U: 3% among ≥15 years old[a] (2013) [32] K: 20% among ≥15 years old[a] (2013) [32]	30% among >15 years old[a] (2012) [29]
HIV+ population on ART (%)	73% among >15 years old[a] [30]	85% among >15 years old[c] (2013) [33]	SA: 30% among 18 to 44 years old[a] Z: 39% among 18 to 44 years old[a]	57% among ≥15 years old[a] [32]	38% among >15 years old[a] [34]

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Table 1. (*Continued*)

Trial indicators	BCPP	*Max*ART	PopART	SEARCH	ANRS TasP
Status of UNAIDS 90/90/90 targets[d]	83% of the HIV+ aged 16 to 64 years in the study population knew their status; of those 87% were taking ART; of those, 96.5% were virally suppressed (HIV RNA<400 copies/ml). The estimated population-level viral suppression among HIV+ adults was 70%[a] [30].	Estimates are unavailable at this time	SA: Estimates are unavailable at this time Z: 54% of the HIV+ aged ≥18 years old in the study population knew their HIV+ status; of those 81% were taking ART[a] [46].	68% of the HIV+ in the study population knew their status; of those 80% had received ART; of those, 86% were virally suppressed (HIV RNA<500 copies/ml). The estimated population-level viral suppression among HIV+ adults was 47% at baseline[a] [32]	At the beginning of the trial, 85.8% were estimated to be diagnosed; of those, 37.1% to be engaged in care and actively on ART; on those 77.8% with a documented viral load and virally suppressed [47]. Note that trial start corresponds to different time points as all clusters were not opened at same time.

[a]Denotes the research study population, which is the population in which the primary outcome and main secondary outcomes (among adults) are being measured. (The eligibility criteria for the research study population are specified in Table 3). Data were collected at baseline by the trial team and extracted from publications and conference abstracts.
[b]Denotes the population living in the trial area; data collected at baseline by the trial team.
[c]Denotes the populations of the countries in which the trials have been implemented; data from national surveys. IQR: Interquartile range; SA: South Africa; Z: Zambia; K: Kenya; U: Uganda; SW-U: Southwestern Uganda; E-U: Eastern Uganda.
[d]Quantitative comparison of the estimates 90-90-90 UNAIDS targets at baseline should be performed cautiously, as there is no standard methodology across trials to compute these figures and is the focus of a separate cross-trial collaboration.

Table 2. Trial research methodologies

Trial	Countries	Design	Primary objective	Primary outcome	Study power	Coefficient of variation between clusters	Estimated trial impact	Duration (average follow-up)[a]	Estimated completion date
BCPP	Botswana	2 arm community-level pair-matched cluster-randomized trial	To evaluate whether expanded ART initiation (initially by high HIV-1 RNA level and higher CD4 threshold, now universal ART), combined with strengthened and expanded HIV testing/linkage and male circumcision services, can significantly reduce cumulative HIV incidence at population-level, in 16 to 64 year old community residents in Botswana.	Cumulative HIV incidence	86% (original parameters and ART initiation criteria) 72% (revised parameters based on observed data, and actual ART initiation criteria over time)	0.26	40% reduction of cumulative HIV incidence in the intervention arm	60 months (average follow-up of 36 months)	October 2018
*Max*ART	Swaziland	2 arm clinic-catchment level - stepped-wedge cluster-randomized trial	To evaluate whether early ART initiation for all HIV+ individuals can improve retention and viral suppression at population-level, in over 18-year-olds, in Swaziland's government-managed health system.	Retention and viral suppression	80%	0.5	6% increase in 1-year retention rate between the control phase and intervention phase	36 months	August 2017
PopART	South Africa, Zambia	3 arm community-level triplet-matched cluster-randomized trial	To determine the impact of two community-level combination prevention packages, both of which include universal HIV testing and intensified provision of HIV ART and care, on population-level HIV incidence	Cumulative HIV incidence	>99% for Arm A versus Arm C comparison (original model parameters and ART initiation criteria); In range 44% to 95% for Arm A versus Arm C comparison (revised parameters based on trial data including on testing and treatment coverage over time)	0.15 to 0.2	60% to 65% reduction in HIV incidence in arm A in years 2 and 3 of intervention (original parameters and ART initiation criteria); 35% to 45% reduction of HIV incidence in arm A in years 2 and 3 of intervention (revised parameters)	54 months (average follow-up of 36 months)	June 2018
SEARCH	Uganda, Kenya	2 arm 2 phase community-level pair-matched cluster-randomized trial	Phase 1: To quantify the impact of early HIV diagnosis and immediate ART using a streamlined care delivery system on the three-year cumulative HIV incidence among adults aged ≥15 years old in rural communities in Uganda and Kenya Phase 2: To quantify the impact of targeted PrEP, targeted HIV testing and targeted care interventions on top of universal treatment and streamlined care on the 3-year cumulative HIV incidence among adults aged ≥15 years old in rural communities in Uganda and Kenya	Cumulative HIV incidence	80% in both Phase1 and Phase2	≤0.4	40% reduction in cumulative HIV incidence (both Phase 1 and 2) in the intervention arm	72 months (follow-up of 36 months in Phase 1 and 36 months in Phase 2)	June 2017 for Phase1 June 2020 for Phase2

Table 2. (*Continued*)

Trial	Countries	Design	Primary objective	Primary outcome	Study power	Coefficient of variation between clusters	Estimated trial impact	Duration (average follow-up)[a]	Estimated completion date
ANRS TasP	South Africa	2 arm community-level cluster-randomized trial	Phase 1: To estimate the feasibility and acceptability of early ART initiation for all HIV+ individuals combined with six monthly home-based HIV testing of all adult members of a community and linkage-to-care services at population-level in 16 and above years of age, in KwaZulu-Natal province in South Africa. Phase 2: To compare how early ART initiation for all HIV+ individuals combined with six monthly home-based HIV testing of all adult members of a community and linkage-to-care services can impact on the reduction in incidence of new HIV infections at population-level in 16 and above years of age, in KwaZulu-Natal province in South Africa.	Cumulative HIV incidence	80%	0.25	A 34% reduction in cumulative HIV incidence in the intervention arm	52 months (average follow-up of 36 months)	June 2014 for Phase 1 July 2016 for Phase 2

ART, antiretroviral therapy; PrEP, pre-exposure prophylaxis.
[a]The trial duration refers to the period between the first day an intervention was provided to a study participant and the last day an intervention was provided to a study participant. The average follow-up refers to the average time a study participant was observed in the context of the trial.

calls). These intervention packages emphasize the key role of an early ART initiation in a wider combination prevention strategy. Furthermore, only a small proportion of those activities is offered in the national standard of care (or offered on a much smaller scale); thus the overall quality and in some cases, efficiency of care delivered to study participants is increased relative to the general population.

Health services are delivered through three main means. First, each trial community is serviced by clinics that provide most of the conventional health activities including HIV care and treatment. In BCPP, *Max*ART, PopART and SEARCH, the trial clinics are government-led (with strengthening of government staff by some trials), whereas in TasP, the clinics are built for the purpose of the trial to bring services closer to people's homes. Second, health services are also delivered through community-based activities like home visits (BCPP, PopART, ANRS TasP, SEARCH), HIV testing in mobile units (BCPP, ANRS TasP), and/or health campaigns (SEARCH). Finally, in some instances, trial participants are referred to government-led health facilities to receive standard of care services that the trials do not provide (e.g. VMMC, sexually transmitted infections care, tuberculosis treatment). The models of care provide examples of how to adapt services to meet the specific needs of patients and the local capacity of the health systems.

3.4 | Trial themes

Table 5 outlines the main themes that are explored in the trials. The scope of the data collected underlines the trials' potential to explore a range of issues including and beyond HIV incidence. All trials carefully monitor the uptake of trial services and the implementation of the HIV care cascade [52]: HIV testing, linkage to care activities, treatment initiation, adherence, and/or viral suppression. Such data will help to assess the trial's success in reaching the UNAIDS 90-90-90 targets for 2020. In addition, all trials document individual health outcomes (some through accessing routine programmatic clinical data). At least a subset of trial participants is observed via repeated screening and diagnostic tests, which may occur in the clinic (BCPP, *Max*ART, PopART, ANRS TasP), at home (BCPP, PopART, ANRS TasP) or at community health campaigns and home (SEARCH). Data such as individual CD4 counts, HIV RNA metrics and results of HIV drug resistance tests, are being accumulated on more than a million people across the trials. Some studies are also using HIV viral phylogenetics to investigate transmission patterns at baseline and over time (BCPP, PopART, SEARCH and ANRS TasP). Importantly, the trials also record the costs of the interventions implemented, and will model their cost-effectiveness, and assess their impact on the operating health systems. The collection of data on human resources, programmatic costs or length of waiting time in clinics will aid in the assessment of the feasibility of integrating universal ART in local health systems. Finally, all trials are investigating social outcomes including facilitators and barriers to accessing HIV care. Besides characterizing the trial populations with standard socio-demographic information, these trials also collect experiences and perceptions of a sample of trial participants, community members and services providers. Such qualitative research provides evidence to understand the acceptability of the UTT

Table 3. Trial population characteristics at baseline

	BCPP	*Max*ART	PopART	SEARCH	ANRS TasP
Cluster selection criteria	Located in one of three populated geographical regions of Botswana Geographically distinct communities, reachable by road Containing a government primary health care facility (clinic or hospital) which provides ART and PMTCT Community size 2500 to 15,000 (ideal 6000) Not site for other research activities that could impact the trial outcomes	Located in the Hhohho region in Swaziland Catchment area of a government primary health care facility which provides HIV care Not a site for another research activity that could impact the trial outcomes	Located in Western cape province of South Africa or Zambia Non-adjacent communities Catchment area of a government primary health care facility which provides HIV and TB care Population ≥20,000 High HIV prevalence Not site for other research activities that could impact the trial outcomes	Located in Southwestern, Eastern Uganda or Western Kenya Non-adjacent communities Served by a government primary health care facility which provides HIV care Accessibility to health centre via maintained transportation route Between 9000 and 11,0000 individuals, not in an urban setting i.e. ≤100,000 Not site for other research activities that could impact the trial outcomes	Located in the Hlabisa sub-district in KwaZulu-Natal province, South Africa Neighbouring communities with clear geographical boundaries and distinct social identities ≥15 km^2 Not site for other research activities that could impact the trial outcomes
Cluster matching and/or stratified randomization and/or restricted randomization criteria	Matching: geographical location, community size, population age structure, baseline access to health services including ART Randomized within matched pairs	Matching: geographical location, clinic-catchment size Stratified randomization	Matching: geographical location, HIV prevalence Restricted randomization: Community size, ART uptake, HIV prevalence	Matching: geographical location (Phase1 and 2), population density (Phase1), migration (Phase1), occupation (Phase1), number of trading centres (Phase1), Phase 1 intervention arm (Phase2), other drivers of HIV incidence (Phase2) Randomized within matched pairs	No matching Stratified randomization: HIV prevalence
Number of clusters	30	14	21 (12 in Zambia and 9 in South Africa)	32 (10 in Southwestern Uganda, 10 in Eastern Uganda and 12 in Kenya)	22
Average cluster population size [range][a]	5785 [2748 to 12,865]	8553 [5326 to 14,868]	44,000 [~16,000-~100,000]	10,450 [8401 – 12,990]	1284 [324 to 2861] (for those aged ≥16 years old)
Intervention population size[b]	105,000 (age 16 to 64 years)	4501	~1000,000	334,512	28,260

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Table 3. (*Continued*)

	BCPP	*Max*ART	PopART	SEARCH	ANRS TasP
Intervention population eligibility criteria[b]	Gave verbal informed consent Is aged ≥16 years Is present at least three nights per month on average in the community over the prior 12 months[a] Is a Botswana citizen (or spouse of citizen)[e]	Gave verbal informed consent Is aged ≥18 years Is attending one of the study facilities Is not pregnant or breastfeeding at time of enrolment Is HIV-positive and ART naïve	Gave verbal informed consent Is aged ≥18 years (Year 1, first months of Year 2); all ages (1 October 2015 onwards)	Gave verbal informed consent Is a member of a study household in the trial area	Gave a written informed consent Is aged ≥16 years Is a member of a study household in the trial area
Research study population size[c]	22,000	4501	43,601	146,906	28,260
Research study population eligibility criteria[c]	Gave written informed consent (or parental permission and child assent if <18 years old) Is aged 16 to 64 years Is present at least three nights per month on average in the community over the prior 12 months Is a Botswana citizen (or spouse of citizen) Is present in one of the 20% randomly selected study households Is not currently incarcerated	Gave written informed consent Is a participant to the intervention population	Gave written informed consent Is a member of the trial population Is aged ≥18 and ≤44 years Is present in one of the 2500 study households randomly selected in each cluster; and intending to remain so for the next 3 years Is not currently enrolled in another ART or PreP study Has not been or is not currently enrolled in an HIV vaccine study	Gave verbal informed consent Is a member of the intervention population Is aged ≥15 years at baseline Is present in a study community for ≥6 months of the year prior the study start	Is a member of the intervention population
Evaluation population size[d]	9000	4501	~33,000	118,038	17,659

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Table 3. (*Continued*)

	BCPP	*Max*ART	PopART	SEARCH	ANRS TasP
Evaluation population eligibility criteria[d]	Is a member of the research study population Is HIV-negative at baseline	Is a member of the research study population	Is a member of the research study population Is HIV-negative	Is a member of the research study population Is HIV-negative at baseline	Is a participant to the research study population Is HIV-negative at baseline

PMTCT, prevention of mother-to-child transmission; ART, antiretroviral therapy; PrEP, pre-exposure prophylaxis.
[a]Cluster population: Total population of a trial cluster (estimated with baseline data).
[b]Intervention Population: Population that is eligible for trial interventions, which for purposes of this definition are testing services in the ANRS TasP, BCPP, PopART and SEARCH trials, or HIV treatment services in the *Max*ART trial (estimated with baseline trial data).
[c]Research study population: Population in which the primary outcome and main secondary outcomes (among adults) are being measured (estimated with baseline data).
[d]Evaluation population: Population in which the trial impact is being evaluated i.e. in which the primary outcome is being measured (estimated with baseline data).
[e]In the BCPP trial, being a Botswana citizen (or spouse of a Botswana citizen) and being present at least three nights per month on average in the community over the prior 12 months are eligibility criteria to access early ART but not to access HIV testing and counselling).

strategies by the general population [29,53-69]. Overall, the analysis of the various themes addressed within these five trials will contribute to understanding the impact of UTT strategies in various contexts as well as inform the generalization of such a strategy to new contexts.

3.5 | Evolutions/adaptations of study design and interventions

Over the past several years, the HIV policy landscape has been in constant evolution, prompting the on-going trials to modify their interventions and strategies. In particular, the trials responded to the WHO recommendations related to ART initiation, preventing mother-to-child transmission and pre-exposure prophylaxis (PrEP) and considered the UNAIDS 90-90-90 targets for 2020. In all studies, the control arms immediately followed the national guidelines. Figure 1 shows the integration of the 2013 WHO ART recommendations in the arms of each trial, with the threshold for ART initiation changing in the control arms from ≤350 CD4 cells/μl to ≤500 CD4 cells/μl: in 2014 for Zambia (PopART), Uganda and Kenya (SEARCH), and in 2015 for South Africa (ANRS TasP, PopART) and Swaziland (*Max*ART). In 2016, the national guidelines moved to universal ART in Botswana (BCPP), Uganda (SEARCH), Kenya (SEARCH) and South Africa (PopART) and both the intervention and control trial arms switched to universal ART in all of these studies. In the same period, other parameters were altered in the trial protocols, especially to adapt to operational challenges (e.g. simplification of procedures of ART delivery, targeting of the most-at-risk population for HIV infection). All PopART communities in Zambia shifted to universal ART as part of a pilot for national roll-out. SEARCH became a two-phase trial; in the second phase, all communities were provided with universal treatment with streamlined care, and communities were re-randomized for targeted PrEP and targeted enhanced testing and care. The BCPP trial started delivering streamlined ART initiation and follow-up in the intervention arm (with same-day ART initiation and fewer clinical visits for stable, virologically suppressed patients on ART). Overall, the five trials have proved to be extremely adaptive to the moving sub-Saharan African political, economic and public health environment, preserving their ability to generate rigorous scientific evidence on UTT effectiveness.

4 | DISCUSSION

We present a comparative assessment of the five ongoing UTT trials in sub-Saharan Africa. We found substantial commonalities but also differences between trials in their multidisciplinary activities. In particular, the trials' principal aims and methodologies align in the following strategies, opportunities and goals.

4.1 | The UTT trials make a plea for combination prevention

The trials deliver a wide range of biomedical, behavioural and structural interventions services to the communities. These strategies build on the plea for combination efforts for HIV prevention and care, which have progressively been gaining influence among scientists and policy makers [63,70-72].

Table 4. Trial interventions

	BCPP			*Max*ART			PopART				SEARCH			ANRS TasP		
	I	C	S	I	C	S	A	B	C	S	I	C	S	I	C	S
Community mobilization																
Specific mobile activities in the community (e.g. roadshows, public announcements from vehicles, door-to-door communication)	x[a]	x	N.A.	**x**	**x**	N.A.	x	x		N.A.	x[a]	x	N.A.	x	x	N.A.
Communication through existing community platforms (e.g. community meetings, civic society activities, schools, clinics)	x[a]	x	N.A.	**x**	**x**	N.A.	x	x	x	N.A.	x[a]	x	N.A.	x	x	N.A.
Health prevention																
Distribution of condoms	x[a]	x	x			x	x	x	x	x	x[a]	x	x	x	x	x
Male circumcision	x[a]	x	x			x	x	x	x	x			x			x
PrEP											x[f]					
PMTCT Option B+	x[a]	x	x			x	x	x	x	x	x[a]	x	x	x	x	x
STI screening	x	x	x			x	x	x		x			x	x	x	x
STI treating	x	x	x			x				x			x			x
TB screening	x[a]	x	x			x	x	x		x	x[a]	x	x	x	x	x
TB treating	x	x	x			x				x	x[a]	x	x			x
Cervical cancer screening			x			x				x	x[a]	x	x	x	x	x
Other HIV opportunistic infections screening	x	x	x			x				x	x[a]	x	x	x	x	x
Screening for chronic illnesses (diabetes and/or hypertension)	x	x	x			x				x	x[a]	x	x	x	x	x
Child care (e.g. immunization, deworming)	x	x	x			x				x	x[a]	x	x			x
Family planning	x	x	x			x				x	x[a]	x	x			x
Antenatal and postnatal care	x	x	x			x				x			x			x
Others (e.g. malaria screening and/or treatment, urgent care, men's health services, dermatological services)	x	x	x			x				x	x[a]	x	x			**x**
HIV testing																
Voluntary HIV testing and counselling	x[a]	x	x	x	x	x	x	x		x	x[a]	x	x	x		x
Provider-initiated HIV testing and counselling in health facilities	x[a]	x	x			x				x	x[a]	x	x			x
Home-based HIV testing	x[a]	x[b]					x	x			x[a]	x		x	x	
HIV testing in mobile units	x										x[a]	x		x[f]	x[f]	
HIV testing during mobile community campaigns	x						x	x			x[a]	x				
HIV treatment[c]																
ART initiation of HIV+ individuals with CD4 count ≤500 cells/μl	x	x	x		x	x		x[d]	x[d]	x[d]		x[e]	x		x	x

Table 4. (*Continued*)

	BCPP			*Max*ART			PopART				SEARCH			ANRS TasP		
	I	C	S	I	C	S	A	B	C	S	I	C	S	I	C	S
ART initiation of all HIV+ individuals	x	x	x	x			x	x[d]	x[d]	x[d]	x[a]	x[f]		x		
Linkage to and retention in care																
Clinic referral upon HIV-positive screen	x	x	x			x	x	x		x	x[a]	x	x	x	x	x
Linkage to care counselling phone calls	x										x[a]	x[f]		x	x	
SMS clinic appointment reminders	x										x[a]	x[f]				
Repeated home visits	x						x	x			x[a]	x[f]		x	x	
Rapid ART initiation (e.g. on the same day as HIV diagnosis)	x			x							x[a]	x[f]				
Adherence support (e.g. support group)	x	x	x				x	x			x[a]	x[f]				
Convenient ART refill process	x										x[a]	x[f]				
Non-cash incentive (e.g. phone airtime)	x															
Transportation voucher	x	x									x[a]	x[f]				
Point-of-care CD4	x	x[b]		x	x						x[a]	x	x	x	x	
Viral load monitoring	x	x	x	x	x					x	x[a]	x[f]	x	x	x	x

This table displays information which is valid up to July 2016. S, Services that should be available in both intervention and control arms as the standard of care according to the national guidelines; C, Services delivered in the trial control arm; I: Services delivered in the intervention arm in all trials except PopART; A, Services delivered in the intervention arm A in PopART; B, Services delivered in the intervention arm B in PopART; N.A., Non applicable. PrEP, pre-exposure prophylaxis; PMTCT, prevention of mother-to-child transmission; STI, sexually transmitted infections; SMS, short message service.

[a]Enhanced provision of these services in the Intervention arm as compared to the Standard of care (S) and Control arms (C).

[b]In the BCPP trial, the home-based testing services including point-of-care CD4 are available to 20% of the study population in control communities, and 100% in intervention communities.

[c]The details of treatment eligibility at different times are to be found in Figure 1.

[d]In the PopART trial, the control arms B and C provide ART initiation of all in Zambia and ART initiation with CD4 count ≤500 cells/μl in South Africa.

[e]Services delivered during the phase 1 of the SEARCH trial.

[f]Services delivered during the phase 2 of the SEARCH trial.

While the UTT interventions have been designed to both lessen the burden of HIV infection and reduce vulnerability to HIV acquisition, their effect in real-world situations remains to be proven. The ANRS TasP trial, the first UTT trial to yield final results, did not demonstrate an effect of offering immediate ART on HIV incidence [73], highlighting the key importance of achieving high rates of linkage to care following HIV diagnosis. The SEARCH trial, still ongoing, recently reported having nearly doubled HIV viral suppression within their study population over two years (from 44.7% to 80.2%), surpassing the UNAIDS 90-90-90 targets [74]. Understanding the magnitude of the effect achieved according to the local context is precisely the aim of the trials. Our appraisal therefore emphasizes the critical monitoring of all the trial services, in order to understand gaps and support the implementation of combination interventions.

4.2 | The UTT trials optimize the HIV care cascade

All trials also consider the optimization of the whole HIV care cascade as key for a successful UTT strategy. Even though the overall trial attention remains on HIV incidence, key secondary outcomes related to the HIV care cascade components have progressively shown their significance when interpreting the trial impact on the HIV epidemic [3,75,76]. In their initial designs, all trials underscored that UTT should aim to increase demand for HIV testing, expand HIV testing services, improve linkage to and retention in care as well as adherence to treatment [77,78]. Interestingly, this focus was subsequently formalized as the 2014 UNAIDS 90-90-90 targets for 2020. As a consequence, even though the trials were underway before the release of the UNAIDS targets, their results may make an important contribution in demonstrating if and how UTT can help to reach those targets and to what degree those targets might prompt a reduction of new HIV infections, in somewhat different HIV epidemic contexts.

4.3 | The UTT trials represent an opportunity to design innovative models of HIV care

In the HIV/AIDS field, models of care have constantly evolved and adapted to the changing needs of communities, patients and to new scientific evidence [79]. Recently, a flurry of new, more-efficient HIV care models has been proposed which challenges the classic standard facility-based model. Among them, the scale-up of ART is leading to one of the most sweeping changes in health care delivery, especially in sub-Saharan Africa [10,80,81]. In this comparative analysis, we document the pragmatic systems and processes of UTT care

Table 5. Themes explored in the collected trial data

	BCPP	*Max*ART	PopART	SEARCH	ANRS TasP
Implementation of the UTT care cascade					
HIV testing	x		x	x	x
Linkage to care	x		x	x	x
Retention in care	x	x	x	x	x
ART initiation and adherence	x	x	x	x	x
Other HIV prevention services (e.g. PrEP, MC)	x		x	x[a]	
Community's health					
HIV disease progression (according to CD4 cell counts and/or HIV viral loads)	x	x	x	x	x
AIDS or TB or other opportunistic infections (total number of cases and incident cases)	x	x	x	x	x
Other health problems (e.g. diabetes, hypertension chronic kidney disease) (total number of cases and incident cases)[b]	x			x[b]	x
ART-associated toxicity and adverse events	x	x	x	x	x
Mortality (overall, HIV-related, child and/or maternal)	x	x	x	x	x
Mother-to-child HIV-1 transmission				x	
Community-level HIV RNA metrics (e.g. community viral load, proportion of individuals with undetectable viral loads)	x	x	x	x	x
HIV drug resistance (transmitted or acquired virus mutations)	x	x	x	x	x
HIV phylogenetics (e.g. direction of HIV-transmission events)	x		x	x	x
Economic and health system impact OF UTT					
Cost per patient per year	x	x	x	x	x
Cost-effectiveness (e.g. modelled cost per infection averted)	x	x	x	x	x
Heath system measures (e.g. time spent from clinic check-in to completion of clinic visit)		x	x	x	x
Community's experiences					
Participant social and behavioural characteristics (e.g. sexual behaviour and prevention practices, quality of life, social networks, experience of HIV-related stigma)	x	x	x	x	x
Participant perceptions and attitudes towards the trial interventions (e.g. universal ART, overall care delivery, access to medical services)	x	x		x	x
Community awareness of the trial interventions		x	x	x	x
Providers attitudes towards the trial interventions	x	x	x	x	x

UTT, universal testing and treatment; PrEP, pre-exposure prophylaxis, MC, medical male circumcision.
[a]Theme explored during the phase 2 of the SEARCH trial.
[b]In the SEARCH trial, other health problems are assessed in both HIV- and non-HIV-infected individuals. In the other trials, they are only assessed in HIV-infected individuals.

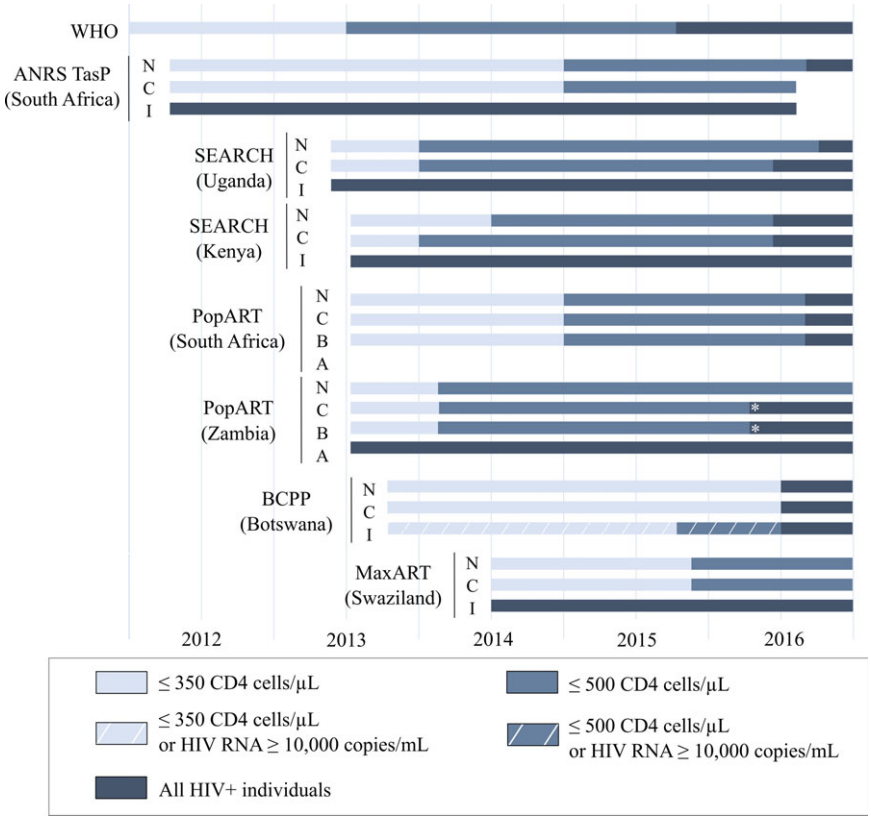


Figure 1. Evolution of the ART eligibility in the UTT trial areas from 1 January 2012 to 31 December 2016. WHO, World Health Organization; N, National recommendations; C, Control arm of the trial; I, intervention arm of the trial; A, Intervention arm A in the PopART trial; B, Intervention arm B in the PopART trial, *shift to universal antiretroviral therapy in the PopART communities in Zambia as part of a pilot for a national roll out.

models that are being field-tested in sub-Saharan Africa and are thus on the forefront of large-scale practice. The trials showcase key interventions which could be integrated in the new models of care, namely community-based approaches for HIV testing with the use of point-of-care HIV tests, rapid facility-based provision of ART, community ART delivery, active follow-up activities, integrated chronic care model with HIV and non-communicable diseases, effective community engagement and close collaboration with the existing health services.

4.4 | The UTT trials give insights on how to generalize UTT to various contexts

To organize health services, including scaled-up access to HIV care and treatment, the trials embrace HIV care approaches that are differentiated by patient type, are people-centred and integrated across diseases and health systems functions. As the recognition of differentiated care and integrated care is growing [48-51], all studies have embraced a common principle, that contextualization is imperative, with integrated services being beneficial in some settings and differentiated care being required in other settings. All trials have chosen their UTT models of care, based on the contexts in which they were implemented, including the possibility of being integrated in the local health care delivery system. Understanding and accounting for the heterogeneous social, political, economic, historical and health systems contextual factors that shape whether and how these UTT strategies work is deemed essential prior to a full-scale rollout of a UTT strategy [59,82]. It is equally important to pay attention to the operational challenges that could result from implementing UTT, including effects of the interventions on individual's everyday lives, health systems and governmental structures [57].

4.5 | The UTT trials are critical to ensure a dynamic interface between policy and research

During their conduct, all trials have regularly exchanged information with their local and/or national health authorities, especially to communicate the trial progresses and the variety of sources of uncertainties that could influence their outputs. This review is an opportunity to provide policy makers with a comprehensive overview of the characteristics of all trials, which are likely to affect the results of the implemented UTT strategies in different contexts. All trials have efficiently adapted their design and interventions to changing guidelines both for ethical reasons and to ensure that their results are of maximal relevance to the public health landscape. Collectively, the trials represent the most relevant information to help answer policy and resource allocation questions. While the plea for UTT is now clear, many countries still need to evaluate the feasibility and cost of adopting such a strategy into their national health system [13]. A clear understanding

of the available evidence will be a key for informed policy formulation.

5 | LIMITATIONS

This analysis has several limitations. First, differences in the trials' design and data collection schemes (Table 3) prevented direct comparison of several indicators at baseline (Table 1). To improve comparison, we provided statistics from both data collected at baseline as well as national indicators (Table S1).

Second, the methods applied are not based on a consensual methodology which would allow a standardized and thus validated direct comparison of the trials. Because no such methods exist yet, we developed, as a consortium, a simple way to comparatively assess all trials. The expertise and experience of the researchers was central to decide which trial components should be compared, at what level of detail, and how to interpret their differences across trials. We opted for a comprehensive description of the trials. We acknowledge that more information on the modelling, economic or social perspectives of the UTT strategies is needed to better understand the trials' interim and final results. Such analyses will be the focus of future collaborative work within our consortium.

Third, when faced with this diversity of UTT approaches, our analysis does not answer the questions arising: are certain study designs more relevant than others? Are specific trial interventions more effective than others? With quantitative data not yet available across trials in similar situations, it is not possible to answer these questions. With this caveat in mind, we conclude that the most appropriate UTT interventions will vary by context and suspect that no single best strategy will emerge.

Finally, in this study, we focused on the five controlled trials measuring the impact of service delivery interventions for UTT in sub-Saharan Africa. We also acknowledge that non-randomized interventions and other operational research experiences will likely be an important source of information, particularly with regard to lessons learnt for implementation. Other novel service delivery methods for UTT are indeed piloted in observational settings but were not captured in this paper [4]. Inclusion of non-randomized studies and evidence may be a focus of future collaborative work.

6 | CONCLUSION

To our knowledge, this is the first detailed exploration of the trials evaluating UTT strategies in sub-Saharan Africa. This *a priori* exercise, i.e. before the individual study findings are released, is not usually performed by investigators. By providing detailed qualitative and quantitative insights about the different trial approaches, our analysis was intended to prospectively build the foundation for more collaborative research on UTT. It also aimed at providing valuable information as the trials are underway and starting to publish process data and findings, to guide as rapidly as possible the strengthening of services for testing and treatment in sub-Saharan Africa, for both individual and public health benefits.

The present study reports on a wide range of attributes of the service delivery models for UTT and highlights the diversity in implementation. The population-level impact of UTT is likely to be context-dependent. The UT^{3}C consortium, with this first paper, intends to set the path for a quicker and deeper understanding on this issue and prepare for future comparison of trial findings and to inform as efficiently as possible public policy in country and internationally.

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COMPETING INTERESTS

The authors declared that they have no competing interests

AUTHORS' CONTRIBUTIONS

François Dabis, Joanna Orne-Gliemann and Delphine Perriat conceived and designed the study. Laura Balzer, Shahin Lockman, Delphine Perriat, Kalpana Sabapathy and Fiona Walsh organized and conducted the data collection. Delphine Perriat wrote the first draft of the manuscript and also produced the figures and the tables. All authors analysed the data, contributed to the writing (and editing) of the manuscript, read and met the criteria for authorship and agreed with manuscript results and conclusions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. National indicators of the countries of trial implementation

Supplementary Table 1: National indicators of the countries of trial implementation

National Indicators	Botswana	Swaziland	South Africa	Zambia	Uganda	Kenya
CENSUS AND DEMOGRAPHIC						
Population census	2,021,000 (2013) [36]	1,250,000 (2013) [37]	52,776,000 (2013) [38]	14,539,000 (2013) [83]	34,634,650 (2014) [84]	44,354,000 (2013) [85]
Rural population (%)	43 (2013) [36]	79 (2013) [37]	36 (2013) [38]	60 (2013) [83]	81,6 (2014) [84]	75 (2013) [85]
Population aged [0-14] (%)	34 (2013) [36]	38 (2013) [37]	30 (2013) [38]	50 (2014) [86]	48 (2014) [84]	43 (2014) [87]
Population aged [15-34] (%)	71 (2013) [88]	34 (2007) [89]	33 (2003) [90]	29 (2014) [86]	17,7 (2014) [84]	32 (2014) [87]
LABOR AND POVERTY						
Unemployment rate among the working-age population/labor force (%)	20 [15-64] (2011) [91]	47 (15+) (2013) [39]	25 [15-64] (2014) [92]	40 [15-49] (2014) [86]	58 [14-64] (2014) [84]	67 [15-49] (2014) [87]
Poverty headcount ratio at national poverty lines %)	15 (2010) [40]	63 (2009) [41]	54 (2010) [42]	61 (2010) [43]	19 (2012) [44]	46 (2005) [45]
EDUCATION AND HEALTH						
Illiteracy rate among adult population (%)	14 [15-49] (2011)[91]	12 (15+) (2011) [93]	19 [15-49] (2011) [94]	26 [15-49] (2014) [86]	28 (10+) (2014) [84]	11[15-49] (2014) [87]
HIV prevalence among adults [15-49] (%)	22 (2015) [95]	29 (2015)[31]	19 (2015) [96]	13 (2015)[97]	7.1 (2015)[98]	5.9 (2015)[99]
Number of people receiving ART	223,974 (2013) [100]	100,138 (2013) [33]	1,600,000 (2012) [101]	556,002 (2014) [102]	750,896 (2014) [103]	656,000 (2013) [104]

3.2. Views of health care workers regarding UTT

The results of this study were dispatched in two manuscripts submitted to PloS One. The first manuscript has been accepted for publication. It is entitled “Implementing universal HIV treatment in a high HIV prevalence and rural South Africa setting – Field experiences and recommendations of health care providers” The second one is currently being revised for publication. It is entitled, “If you are here at the clinic, you do not know how many people need help in the community.”: perspectives of home-based HIV services from health care workers in rural KwaZulu-Natal, South Africa in the era of Universal Test-and-Treat” Both manuscripts are provided at the end of this section.

3.2.1. Background

Insufficient and delayed engagement in care is affecting the HIV response. For a UTT strategy to be successful, optimizing the whole HIV care cascade is paramount as all people living with HIV and whose viral load is not suppressed are likely to contribute to new infections [157, 185]. Evidence accumulates on the feasibility of interventions that aim at testing everyone and treating all those identified HIV-positive, supporting the large-scale implementation of an arsenal of testing, linkage and treatment services [27]. Yet, their implementation demands the buy-in of frontline HCWs who will oversee their delivery. It is yet unknown how HCWs exposed to UTT understand and claim ownership over UTT strategies. The TasP trial provides a unique opportunity to investigate their opinions on the matter, therefore informing policy-makers, program planners and other health authorities of the key components of a comprehensive UTT strategy to benefit people's health.

3.2.2. Objective

We explored the field experiences and perceptions of local HCWs regarding home-based services for HIV testing and support for engagement in care, as well as clinic-based universal ART, as opportunities to improve the cascade of care of people living with HIV in rural South Africa within the framework of the UTT approach developed for the TasP trial.

3.2.3. Methods

We conducted a cross-sectional mixed-methods survey among HCWs from the TasP trial and from local government clinics, using self-administrated questionnaires, semi-structured interviews and focus group discussions (Table 1) (Figure 30,Figure 31) (See Appendices 6.2 and 6.3).

Table 1: Methodological details of the cross-sectional TasP Health care professionals survey, ANRS 12249 TasP trial, KwaZulu-Natal, South Africa

	Quantitative study	**Qualitative study**
Timeline	April 2016	May-July 2016
Sampling	All HCWs involved in the TasP trial service delivery (n=104) or working in the HIV services of the local government primary healthcare clinics in Hlabisa sub-district (n=78)	Selection of participants among the staff met during the quantitative study (n=41)
Data collection	• Self-administrated structured paper-based questionnaires of 30 minutes • Data collected by researchers in study participants' workplaces during staff meetings • Data captured with RedCap®	• SSIs (60 -90 min) + FGDs (120 -160 min) • Data collected by four qualitative interviewers in isiZulu in study participants' workplaces • Data audio-recorded, transcribed in isiZulu and translated to English
Study population	• Home-based HIV services in the TasP trial (n=57) • Clinic-based HIV services in the TasP trial (n=33) • Clinic-based HIV services in the local government programme (n=56) → Total number of participants: 146	• Home-based HIV services in the TasP trial (5 SSI, 1 FGD) • Clinic-based HIV services in the TasP trial (8 SSI, 2 FGDs) • Clinic-based HIV services in the local government programme (5 SSI) → Total number of participants: 18 SSI, 3 FGD
Data collected	Demographic details, experience of HCWs in providing HIV services, perceptions of various UTT interventions, job satisfaction.	Roles and motivations in HCWs' work, challenges faced and perceptions of the strengths and weaknesses of the interventions delivered in the TasP trial, opinion on the scale-up of those interventions in the whole of Hlabisa sub-district and beyond
Data analysis	Descriptive statistics with R software	Inductive approach based on descriptive thematic coding using NVivo® (See Appendix 6.4)

HCW: Health care worker, UTT: Universal test and treat, SSI: Semi-structured interview, FGD: focus group discussion



Figure 30: Government nurses and ART counsellors filling in the self-administered quantitative questionnaires of the TasP Health care professionals study, ANRS 12249 TasP trial (Photo credit: Delphine Perriat)



Figure 31: Recruitment of participants to TasP Health care professionals study, ANRS 12249 TasP trial (Photo credit: Delphine Perriat)

3.2.4. Principal results and discussion

3.2.4.1. Home-based services for HIV

In our study area located in the rural KwaZulu-Natal province of South Africa, HCWs assessed home-based HIV services as highly feasible and acceptable. They therefore pronounced themselves in favour of their large-scale implementation in the routine health system, including for HIV testing and counselling, as well as support for linkage to and retention in care. They pointed out the potential of privileged provider-patient relationship built at home to inspire action in people and provide them with support to take up and maintain access to HIV services. As HCWs expressed concerns about the ability of home-based services to answer the HIV care needs of some vulnerable population groups (e.g. people working outside of their home during the day, people who fear HIV-related stigmatization), they build on the plea for differentiated and person-centred care to adapt services to people's diverse healthcare needs [32]. These findings come at a time when the last decade has highlighted major gaps in the availability, accessibility and quality of the heath workforce in many resource-limited countries [186-188] and home-based HCWs represent a true opportunity to shape the development of a new workforce and rationalize health care demands [28, 29].

3.2.4.2. Clinic-based universal ART

ART for all people living with HIV is at the core of universal test-and-treat strategies. In our study area, located in the rural KwaZulu-Natal province of South Africa, HCWs pronounced in favour of implementing immediate ART to benefit the health of the communities they serve. They yet pointed out that its large scale implementation would likely be more complex than the simple removal of eligibility criteria for ART initiation. Those who had the opportunity to experiment with immediate ART within the TasP trial reported that most people living with HIV were willing to initiate ART, but that asymptomatic patients were more likely to require individualized support to understand the rationale of entering a life-long therapy. HCWs also noted that they interacted differently with their patients, moving out from asking themselves "Is my patient eligible for ART?" to "How can I encourage my patient to start ART?". Our study clearly points out that considering the shift in patients' healthcare expectations and HCWs practices is key for the success of the treatment component of UTT strategies. These findings come at a time when countries are largely rolling out immediate ART, including South Africa. Decision-makers are encouraged to channel immediate ART implementation by empowering service delivers with proper training and building an enabling environment with a supporting network of HIV care services in order to make the most of ART for all.

3.2.5. Role of the PhD candidate

Together with three other researchers, including one of my PhD directors, I designed the TasP ancillary study among Health care professionals. I participated in writing the study protocol and data collection tools. After receiving ethical approval from the Biomedical Research Ethical Council (BREC) of the University of KwaZulu-Natal in March 2016, I co-coordinated with Mélanie Plazy the fieldwork of the study between April and July 2016. I collected the quantitative data among HCWs, captured it using the Research Electronic Data Capture (REDCap) software and analysed it with R software version 3.0.1. I supervised the qualitative data collection team that consisted in four qualitative interviewers. I performed the qualitative data analysis with the NVivo software (version 11, QSR International Pty Ltd., Doncaster, Victoria, 3108, Australia), in collaboration with Mélanie Plazy. I wrote the first draft of the work on home-based services. Melanie Plazy wrote the first draft of the work on early ART.

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TITLE

Full title: "If you are here at the clinic, you do not know how many people need help in the community.": perspectives of home-based HIV services from health care workers in rural KwaZulu-Natal, South Africa in the era of Universal Test-and-Treat

Short title: Perspectives of home-based HIV services from health care workers in rural South Africa in the era of UTT

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TRIAL REGISTRATION

The registration number of the ANRS 12249 TasP trial on ClinicalTrials.gov is NCT01509508 (https://clinicaltrials.gov /ct2/show/NCT01509508).

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ABSTRACT

Background: Limited engagement in clinic-based care is affecting the HIV response. We explored the field experiences and perceptions of local health care workers regarding home-based strategies as opportunities to improve the cascade of care of people living with HIV in rural South Africa as part of a Universal Test-and-Treat approach.

Methods: In Hlabisa sub-district, home-based HIV services, including rapid HIV testing and counselling, and support for linkage to and retention in clinic-based HIV care, were implemented by health care workers within the ANRS 12249 Treatment-as-Prevention (TasP) trial. From April to July 2016, we conducted a mixed-methods study among health care workers from the TasP trial and from local government clinics, using self-administrated questionnaires (n=90 in the TasP trial, n=56 in government clinics), semi-structured interviews (n=13 in the TasP trial, n=5 in government clinics) and three focus group discussions (n=6-10 health care workers of the TasP trial per group). Descriptive statistics were used for quantitative data and qualitative data were analysed thematically.

Results: More than 90% of health care workers assessed home-based testing and support for linkage to care as feasible and acceptable by the population they serve. Many health care workers underlined how home visits could facilitate reaching people who had slipped through the cracks of the clinic-based health care system and encourage them to successfully access care. Health care workers however expressed concerns about the ability of home-based services to answer the HIV care needs of all community members, including people working outside their home during the day or those who fear HIV-related stigmatization. Overall, health care workers encouraged policy-makers to more formally integrate home-based services in the local health system. They promoted reshaping the disease-specific and care-oriented services towards more comprehensive goals.

Conclusion: Because home-based services allow identification of people early during their infection and encourage them to take actions leading to viral suppression, HCWs assessed them as valuable components within the panel of UTT interventions, aiming to reach the 90-90-90 UNAIDS targets, especially in the rural Southern African region.

Keywords: HIV, health care worker, home-based care, South Africa, qualitative, quantitative

INTRODUCTION

Coverage of HIV testing and treatment remains sub-optimal, especially in low–income countries, which carry the heaviest HIV burden worldwide [1]. To fast track the response to the pandemic, UNAIDS in 2014 set out the 90-90-90 targets (namely, that 90% of people living with HIV know their status; that 90% of all people with diagnosed HIV infection receive sustained antiretroviral treatment (ART); and that 90% of all people receiving ART have viral suppression). In 2015, the World Health Organization (WHO) recommended ART for all people living with HIV [2]. In this context, the Universal Test and Treat (UTT) strategy aims at offering regular HIV testing and counselling to an entire population, and ART to all those living with HIV.

Several research projects, including randomized controlled trials in Southern and Eastern Africa, are currently accumulating evidence on the feasibility, acceptability and effectiveness of UTT strategies to fight the HIV epidemic [3]. UTT can include a large and diverse range of HIV-related services at each step of the HIV care cascade, starting from community mobilization and prevention, to testing and linkage to care, through to treatment and retention in care. These services can be delivered at home, within the community and/or in clinics [4].

Historically and worldwide, the HIV care model has been mainly facility-based, with patients presenting themselves for HIV testing and treatment [5]. Yet, access to facility-based HIV care has been sub-optimal especially in rural and resource-constrained settings [6], and the role of home-based services has been increasingly promoted [7]. Home-based services including the provision of HIV testing and counselling within households, or home visits to support linkage to care and retention have been shown to be highly acceptable by patients, families, communities and health care workers (HCWs) [8] and to improve the uptake of HIV testing [9, 10], linkage to care and treatment adherence rates [11] while being three to four times cheaper

than clinic-based approaches [12, 13]. However, the high initial operating costs, especially in terms of human resources and logistics have deterred decision-makers from officially integrating home-based services in the local and national health care systems. Home-based services have thus been facing various challenges such as inadequate training, support and supervision of HCWs [14], poor service coverage, due to the uneven geographical distribution of HCWs [15], and poor recognition of the value of HCW's work [7, 16]. Regardless, WHO recently reemphasized the prospects of home-based models for HIV control, especially in rural and highly HIV prevalent areas involving lay care providers [17-20].

South Africa is facing the biggest HIV epidemic in the world (7 million of people are living with HIV) [21]. Despite intensive efforts, HIV testing and specifically repeat testing, linkage and retention in care in the local and national HIV care programs remain sub-optimal [11, 22]. The national government has been supporting local initiatives for a diversification of health interventions including home-based HIV services, especially in rural areas [13, 23-25]. However home-based services have not yet been standardized and integrated within the national health system [26]. In September 2016, South Africa adopted a policy of providing ART to everyone living with HIV, posing a challenge to the current health system. Home-based services could be a valuable component to address the increased demands for HIV care provision [27, 28].

The long-term benefits and sustainability of home-based services as part of a UTT strategy are being explored in population-based trials currently ongoing in Southern and Eastern Africa [3]. Among them, the first to yield results was the ANRS 12249 TasP (Treatment-as-Prevention) trial, a cluster-randomized trial implemented in rural KwaZulu-Natal, South Africa [29, 30]. The UTT strategy implemented within the TasP trial included a home-based approach for HIV testing and support for linkage and retention in care. It was highly successful in terms of HIV testing coverage within these poor and disadvantaged rural communities (92% home-based HIV testing and counselling uptake among those offered the services) [31] and also contributed to significantly increase rates of linkage to care [32]. While these findings suggest support for the large-scale implementation of home-based services, implementation of this approach demands the buy-in of frontline HCWs who will oversee delivery of those services. The TasP trial provides a unique opportunity to investigate how HCWs view home-based services in the context of a UTT strategy. We explored the experiences and perceptions of local HCWs regarding home-based HIV services as strategic components of the arsenal of UTT

interventions, aiming at improving the cascade of care of people living with HIV in rural South Africa.

METHODS

Study setting/context: the ANRS 12249 TasP trial

The TasP trial was implemented by the Africa Health Research Institute (AHRI) (former Africa Centre for Population Health) from March 2012 to June 2016 in Hlabisa sub-district (northern KwaZulu-Natal), in a rural area with approximately 28,000 isiZulu-speaking resident adults [33]. The HIV prevalence in the sub-district is one of the highest in the world, with around 29% of adults infected with HIV [34]. The trial aimed to investigate whether immediate ART initiation offered to all HIV-positive individuals, identified through home-based HIV testing, reduced HIV incidence in the area.

The UTT strategy implemented in the TasP trial had two main components: 1. Home-based HIV testing and counselling offered every six months to all adults of 16 years and above who reside in the trial area, and referral of those identified HIV+ to local trial clinics for HIV care, 2. ART initiation in local trial clinics (initiation regardless of CD4 count in the intervention arm, vs initiation according to the South African guidelines, i.e. at a CD4 count $\leq$ 350 cells/μL prior January 2015, then CD4 count $\leq$ 500 cells/μL in the control arm). Additional services were implemented for HIV-positive individuals, namely: phone and home-based support for linkage to care targeting individuals who had not visited a trial clinic within three months after identification of their HIV positive status; and phone and home-based support for retention in care targeting individuals three months after a missed appointment in a trial clinic. These services were delivered by a wide range of skilled HCWs (Fig1).

Fig1. Study population

ART: antiretroviral treatment, TasP: ANRS 12249 Treatment-as-Prevention trial

The trial area was also served by the HIV treatment and care programme in the local government clinics of Hlabisa sub-district, in which counsellors offer HIV testing and nurses offer treatment to people in local government clinics [35]. Additionally, a network of community volunteers with limited training in healthcare, referred to as Community Care

Givers (CCGs), regularly visit people's homes to encourage them to visit the clinics to get healthcare, including HIV-related healthcare [36, 37].

Study design, study tools, study population and sample

We conducted a cross-sectional mixed methods study in the TasP trial area in South Africa. The quantitative component of the study, which was conducted in April 2016 aimed at measuring the global appreciation of HCWs regarding the acceptability and feasibility of home-based HIV services as part of a UTT strategy. The qualitative component conducted between May and July 2016 aimed at describing the reasons behind such perceptions as well and the specific personal experiences of HCWs [38]. All HCWs involved in the TasP trial service delivery (n=104) and working in the HIV services of the 17 government primary health care clinics in Hlabisa sub district (n=78) were invited to participate in the quantitative study. The qualitative component of the study consisted of semi-structured individual interviews (SSI) and focus-group discussions (FGD). Participants to the qualitative component were selected among the staff met during the quantitative component of the study, and based on three main criteria (age, years of experience, high versus low clinic volume) to capture diverse professional contexts. HCWs belonged to three different groups depending on the services they delivered: home-based HIV services in the TasP trial, clinic-based HIV services in the TasP trial or clinic-based HIV services in the local government programme (Fig1). A total of 18 SSIs (13 with TasP staff and 5 with government staff) and three FGDs with TasP staff (6 to 10 participants) were conducted (Table 1).

Data collection

Quantitative component: Self-administrated structured paper-based questionnaires were distributed by the researchers to the staff working in the HIV services of the government clinics and to the staff of the TasP trial during their respective staff meetings in their workplace. Logistical help was provided by AHRI to inform the Department of Health (DoH) and TasP managers of the study, arrange for the staff availability to participate in the study and introduce the researchers to the staff. Prior to questionnaire completion, the researchers briefly presented the study to participants, highlighting that completing a questionnaire was voluntary and anonymous. The completion of a questionnaire lasted for up to 30 minutes. Participants then inserted the questionnaire in a closed box to preserve anonymity. All questionnaires were in English and had the same structure: (1) a section on demographic content (2) questions on the experience of HCWs in providing HIV services (the content of this section was adapted to the

specificities of the staff profession), (3) questions eliciting their perceptions of various UTT interventions, and (4) questions measuring their job satisfaction. The instrument was piloted with staff of the TasP trial, which resulted in some minor changes related to item wording. Data were captured using the Research Electronic Data Capture (REDCap) software.

Qualitative component: Four local experienced qualitative interviewers were recruited to carry out FGDs and SSIs in isiZulu. They received specific training on interviewing techniques with staff members, to minimize bias from respondents when questioned about the institution they work for. SSIs lasted for 60 to 90 minutes, and FGDs for 120 to 160 minutes. They were held either in a closed meeting room at AHRI for the TasP staff, or at a place of convenience for the participants from the government clinics. Semi-structured guides for the SSIs and FGDs were designed to fit the specificities of the range of professions interviewed. Participants were asked about their roles and motivations in their work, the challenges they faced and their perceptions of the strengths and weaknesses of the interventions delivered in the TasP trial, as well as their opinion on the scale-up of those interventions to the whole of Hlabisa sub-district and beyond. Data were audio recorded, transcribed in isiZulu and translated to English. The quality of the translations was checked by the most experienced qualitative interviewer. During the whole data collection, interviewers were supervised and coached by researchers who provided them with professional support to manage their tasks and facilitate fieldwork.

Analysis process

Quantitative component: This publication explores quantitative data extracted from the third section of the study questionnaire, regarding the perceptions of HCWs on home-based HIV services, including HIV testing and personalized support for linkage to care. Respondents rated the degree to which they agreed or disagreed with statements using a five point ordinal Likert scale (totally disagree, partially disagree, no opinion, partially agree, totally agree). Results were analysed using R software version 3.0.1.

Qualitative component: An inductive approach based on descriptive thematic coding was used to explore the qualitative data. All transcripts were entered in a qualitative data analysis management software (NVivo version 11, QSR International Pty Ltd., Doncaster, Victoria, 3108, Australia). Codebooks were developed using an iterative process: initial codes matched the broad research themes that we used in the interview and focus group discussion guides, then were expanded with codes, drawn from the data, reflecting the participants' own terms and semantics, and discussed within the team, including qualitative interviewers and researchers, to

triangulate input. The hierarchical coding framework contained five main codes, with four levels of branching each, and a total of over 60 sub-codes. Examples of main codes are: organization of resources to meet the HIV health needs of the community, ability of the organization to deliver HIV services, attitudes and perceptions of community members regarding seeking and accessing care. This publication focuses on the data coded using these sub-codes on three types of home-based services: HIV testing and counselling, support for linkage to care, and support for retention in care.

Ethics

Formal ethics approval was provided by the Biomedical Research Ethical Council (BREC) of the University of KwaZulu-Natal on March 18, 2016. All participants voluntarily gave their informed written consent.

RESULTS

Overall, 146 quantitative questionnaires were completed (overall response rate 80%: 86% for TasP staff and 72% for government staff). Reasons for non-completion of the questionnaires were mainly annual or sick leave and unavailability at the time of the clinic visit. Only two were explicit refusals. As the South African health workforce is predominantly female (over 90% in KwaZulu-Natal [39]), most respondents were women in both the quantitative (n= 81, 76%) and the qualitative (n=38, 92%) studies. Participants ranged in age from 25 to 74 years old in the quantitative study (median age = 34 years, interquartile range (IQR) = [30-40]) (Table 1) and from 25 to 72 years old in the qualitative study (median age = 37 years, IQR = [32-53]) (Table 2 and Table 3).

Fig2. Perceptions of HCWs on HIV services delivery (n= 146)

ART: antiretroviral treatment, * The variable has 2 missing values, ** The variable has 1 missing value, *** The variable has 3 missing values, **** The variable has 4 missing values.



Table 1: Personal information in quantitative research participants (N= 146)

	N (%)
Gender (N=146)	
Male	65 (24%)
Female	81 (76%)
Median age [IQR] (years) (N=134)	34 [30-40]
Professional role (N=146)	
TasP home testing-fieldworkers	38
TasP home linkage-fieldworkers	6
TasP home retention-fieldworkers	8
TasP home services managers	5
TasP clinic nurses	15
TasP clinic ART-counsellors	15
TasP clinic services managers	3
Government clinic nurses	40
Government clinic testing-counsellors	16

IQR: interquartile range

Table 2: Personal information in research participants of qualitative semi-structured interviews (N=18)

Position/Cadre	Sex	Age (years)	Experience in HIV care (years)
Home-based HIV services in the TasP trial			
Home linkage-fieldworker 1	F	40	9
Home linkage-fieldworker 2	F	53	10
Home retention-fieldworker	F	41	14
Home services manager 1	F	32	3
Home services manager 2	F	42	12
Clinic-based HIV services in the TasP trial			
Clinic nurse 1	F	35	8
Clinic nurse 2	F	53	8
Clinic nurse 3	F	34	6
Clinic nurse 4	F	71	10
Clinic ART counsellor 1	F	46	16

Clinic ART counsellor 2	F	31	9
Clinic trial manager 1	F	39	8
Clinic trial manager 2	F	44	11
Clinic-based HIV services in the local government programme			
Clinic nurse 1	F	47	17
Clinic nurse 2	F	63	7
Clinic nurse 3	F	50	6
Clinic services manager 1	F	31	3
Clinic services manager 2	F	56	17

F: female, M: male

Table 3: Personal information in research participants of qualitative focus group discussions (N=23)

Position/Cadre	Number of participants	Sex	Median age [range] (years)	Median experience in HIV care [range] (years)
Home-based HIV services in the TasP trial				
Home testing-fieldworkers	10	9F, 1M	31 [26-41]	6 [3-13]
Clinic-based HIV services in the TasP trial				
Clinic nurses	7	6F, 1M	46 [34-71]	7 [5-9]
Clinic ART counsellors	6	5F, 1M	45 [29-58]	11 [6-14]

F: female, M: male

1. Home-based services have the potential to draw into care people who have slipped through the cracks of the existing health care system

Home-based services are perceived as highly acceptable and very convenient

Over 90% of the quantitative study participants affirmed that home-based services are acceptable by the population they serve (Fig2). HCWs who delivered such services within the TasP trial explained during the qualitative interviews that community members were usually agreeable to them entering their household and appreciated receiving HIV services in their homes.

"People were happy that we visited them in their homes; giving them information, testing them for HIV. They were also happy to access the trial clinics, which were close by" (SSI, TasP clinic ART-counsellor 2)

"I can say that people from rural areas are not rude. […] It never happened that we would arrive at a participant's home, and the participant would refuse to talk with us. People from rural areas have respect." (SSI, TasP home linkage-fieldworker 2)

Additionally, home-based services were seen as a possible means to overcome some common structural and individual barriers to facility-based health services: people are spared walking long distances, paying for transport to visit a clinic, or queuing for hours in the waiting room and risking to be seen by community members.

"According to me, it (meaning home-based HIV testing) *is a good thing, because some (trial) participants were afraid to go to the [government] clinic to get tested, and to queue for a long time to be seen. It happens that people are sick and afraid to go to clinic to know his/her status. But when we go to people's home (in the TasP trial), we request everyone individually to come and test with us. We don't choose. Then the participants will know their status." (FGD, TasP home testing-fieldworkers, participant 6)*

Home-based services enable a strong support for HIV care due to family closeness and connectedness with HCWs

All TasP HCWs who delivered services at home mentioned during the interviews the role of the family in people's acceptance of HIV services. They observed powerful group dynamics at home, with family members encouraging each other.

"What's good about the TasP trial is that, when we arrive at participants' home, we sometimes find people that don't want to be tested for HIV. But if they see us testing one of their family members, they change their minds and push each other to be tested […]. It becomes easier for them" (FGD, TasP home testing-fieldworkers, participant 7)

Many HCWs emphasized the strong interpersonal skills they had to display to engage in extended one-to-one talks with people in their homes. They expressed the rewarding feeling they got from helping people most in need.

"That's why I love linkage activities. Because it has helped many people who were sitting at home. […] Once, a participant (to the TasP trial) was happy and said to me "Wow, you are the one who helped me. I was dead and afraid, but now I am alive and not afraid." (SSI, TasP home linkage-fieldworker 2)

"You find that a grandmother's child has been helped because you encouraged him/her to go to the clinic. The grandmother would have failed on various occasions to convince her child to go to the clinic […]. But then you come in their home and help the child. Then the grandparents will love you because they see the results of your work." (SSI, TasP home linkage-fieldworker 2)

Home-based services are conducive to promoting entry and retention in HIV care

Home-based HIV services were perceived as promising add-ons to boost the HIV care cascade. During the qualitative interviews, several HCWs explained that HIV testing at home allowed people to learn about their positive HIV status, even those that wouldn't have voluntarily sought HIV testing. Others underlined the potential of home visits to diagnose people early in the course of their infection, therefore empowering them to seek healthcare. Individuals receive personalized support and are encouraged to build enough self-confidence to enter and be retained in care.

"I loved home testing because some people are not aware that they are HIV-positive. By testing for HIV at home, they get to know their statuses earlier. This allows them to make informed decisions on how they will continue living their lives." (SSI, TasP clinic nurse 4)

"Some trial participants were referred by home testing-fieldworkers for counselling during home visits. They would realize that, the reason why they are sick is that they now have the virus. They find out about it when they are told there [at home]. Then they come for help [at the clinic]. You can see that, as time goes by, people who have not yet accepted [their positive HIV status] start saying: "Oh! All these illnesses that I had, it was because I was infected by HIV and not aware of it. I am now okay and feel well." (FGD, TasP clinic ART-counsellors, participant 1)

Additionally, many TasP HCWs noted that providing respectful HIV services at home contributed to building people's trust towards clinic-based health care providers.

"People (meaning some trial participants) *say that they come to the trial clinics because of the way home testing-fieldworkers showed them care during the home visits. They assumed that they would receive the same care at the clinic than the one they received from the fieldworkers at home. The way fieldworkers behave and care for them is one of the reasons why they come to the clinics." (FGD, TasP clinic ART counsellors, participant 2)*

Government HCWs specifically mentioned how teaming up with CCGs, who move about in the community, including to people's homes, contributes to tracking the lost-to-care populations to encourage them to use clinic-based services

2. Home-based services are not a magic bullet

Home-based services don't reach everyone

Overall, TasP home fieldworkers explained that the main reason for not being able to offer home services to community members was that people were not present in their households at the time of the home visits (e.g. people were working, especially men, were at school or had moved away to another area). Home fieldworkers underlined that home visits were never refused when prior agreement had been provided during a phone call.

> *"We had a challenge of finding males because they were not found in their homes during the day. […]. But those who were at home at the time of home visit, we were able to find them. There isn't a difference in testing [between males and females]. Once you find the participant, s/he will accept [as] they are taught that they should take care of themselves."(SSI, TasP Home services manager 1)*

Besides, several TasP HCWs reported circumstances in which their services were not appreciated. Some people refused services, claiming that they needed more help than the trial protocol provided (e.g. food or transport to go to the clinic). Others lied about their identity to avoid being offered services. And others expressed their annoyance or dislike over repeated home services visit, specifically regarding repeat HIV testing, every six months.

> *"Sometimes, when you get inside [a participant's house], [a family member] will come after you have introduced yourself. And s/he will ask: "Who do you want to speak with?" Then s/he will say: "S/he is not here." Then you will find out that this person you are talking to is actually the one you are looking for (to offer him/her testing). And then the whole family will laugh at you and you will end up looking like a fool." (SSI, TasP home linkage-fieldworker 1)*
>
> *"It happened that you visit the house of someone that has already tested positive for HIV in a previous trial round. So s/he will say: "You have found me last time and tested me positive. So, what are you here to do now? I now know my status. There is no need to keep coming back to me. You should continue with others who have not tested yet or those who are not positive." (FGD, TasP home testing-fieldworkers, participant 9)*

Home-based services do not always preserve full confidentiality and freedom of choice

Some TasP HCWs reported during interviews having witnessed people's discomfort and refusal of HIV home services. Certain people feared being seen in contact with an institution working on HIV; their neighbours would label them as living with HIV. In the quantitative study, over half of HCWs expressed concerns about a possible lack of confidentiality of home-based HIV services (Fig2). Such a result was explained by HCWs as the fact that, during home-based HIV testing, unintentional HIV status disclosure could occur in the absence of soundproof rooms in poor households, or because time of counselling may be longer for people with a positive HIV diagnosis, or also because a positive HIV diagnosis could be read on people's faces. Regarding support for linkage and retention in HIV care, a confidentiality breach could happen as the services specifically target people living with HIV.

> *"If people are tested at the clinic, they receive their results there and cry all the way home. And they arrive at home in a good state. But if you test them at home, some just fail to act as if they are okay. When s/he goes out of the room, you can just see that s/he is not okay. And it means that things did not go well inside. So, at home the confidentiality might be compromised." (FGD, TasP home testing-fieldworkers, participant 3)*

Some TasP HCWs who delivered services at home mentioned the important role that family members could play in people's acceptance of health services. Individuals could feel forced into accepting or refusing services. TasP HCWs talked about the discomfort of standing out of the family crowd, and the fear of feeling obligated to report to the family on the outcome of the discussion with the HCW, especially among young adults and women who live under their husband's control.

> *"The other challenge that [young people] have about testing at home, is that if they test, parents or old people want to know his/her results when s/he is done." (FGD, TasP home testing-fieldworkers, participant 5)*

Further, some TasP HCWs raised the issue of possible coercion of people by HCWs into accepting home-based HIV services.

> *"Some community members feel forced by the home linkage-fieldworkers to come [to the clinic]. There is a slim chance that those people will then continue attending care. Indeed, you put them in class at the first clinic visit where they learn. But then they leave and never come back to the clinic, because they were forced to come at first. They just came so that anyone who was on their case (referring to the home linkage-fieldworkers) would just leave them alone." (FGD, TasP clinic ART counsellors, participant 1)*

Nevertheless, the quantitative study showed that more than four out of five HCWs (87%) disagreed with the fact that home-based HIV testing could force people into accepting services (Fig2).

Home-based services entail challenging working conditions

Several TasP HCWs mentioned how they were emotionally affected while assisting very poor and disadvantaged people with HIV testing or support for linkage and retention to care services.

> *"A thing that I can say was a bit challenging was when I found a participant who was sick and I failed to assist him/her. […] S/he was sick and s/he had no means to get to the clinic. […] I had to leave that participant sleeping there at his/her home. S/he was not able to walk to the clinic and I was not allowed to bring him/her there in our trial cars." (SSI, TasP home-linkage-fieldworker 2)*

TasP HCWs also narrated unpleasant, and even scary, situations they faced while delivering services in the community. All TasP HCWs talked about the daily operational challenges, which result from working in a rural, poor and remote area with scattered households. Many of them regretted that vehicles were sometimes unreliable, despite them being essential to reach people's homes. Moreover, some explained that they feared for their safety (e.g. dog bites, physical aggressions). They often held the line management accountable for their low training and operational support.

> *"Some community members in the community that I was working with, told me […] that they wanted to rob me and they wanted to even take the material that I worked with. They wanted to abuse me because I kept on coming to do the one and the same thing. I was in danger and had to make sure that when I walked, I walked with males and not in dark or isolated places." (SSI, TasP home linkage-fieldworker 7)*

Additionally, government HCWs regretted the lack of an established policy framework for home-based services.

> *"There are [government] clinics that have an outreach team which is a team with a sister* (meaning a professional nurse)*, CCGs and some nurses that visit people at home. But in our clinic, we don't have such a team. We are hoping that, in the future, we are going to have one because, in the establishment* (meaning in the official health district programme)*, it does state that there should be an outreach team, but we still don't have it. […] I think the Hlabisa department of health has a problem with transport. It seems that they don't have enough cars. But each outreach team needs a transport." (SSI, Government clinic nurse 2)*

3. Home-based HIV services promote re-thinking the current model of care towards differentiated care

Support for the integration of home-based HIV services in the local health system, despite organizational challenges

All HCWs supported the further implementation of home-based services for HIV testing and support for linkage and retention in care as part of the local model of care. Some government HCWs also shared their willingness to participate in the home activities if given the opportunity.

> *"If you are here at the clinic, you do not know how many people need help in the community. I think we do need to increase mobile clinics that visit people at home. […] Because we will also like to work within homes, but we can't because we must be here at the clinic" (SSI, government clinic nurse 1)*

In the quantitative study, a large majority of HCWs expressed their support for the implementation of yearly HIV testing campaigns (95%) and a linkage to care services programme (86%) (Fig2).

Some HCWs were also convinced that the integration of home-based HIV testing in the local health system would participate in decreasing HIV-related discrimination and normalizing regular HIV testing, as all households would be visited.

> *"I think the HIV-related discrimination could be decreased with home-based HIV testing because participants could see the importance* of testing *[…] Even if they don't like being tested for HIV, they will do it, simply because it is done to the whole community. They will not want to be the only one who is not doing it." (FGD, TasP home testing-fieldworker, participant 7)*

Yet, many HCWs pointed out organizational challenges that would ensue from the integration of home-based HIV services in the local HIV programme. In the quantitative study, most participants expressed concern about a lack of human resources for implementing home-based services in the local health system (93% regarding HIV testing and 86% regarding support for linkage (Fig2)). During the interview sessions, HCWs formulated advice for implementers: involve local leaders ("izindunas" and "ward councillors") to inform the community on the programme, dedicate enough financial means, hire a big enough workforce and provide them with proper means (e.g. transport, equipment), adequate training and continuous on-the-job support and officially recognize the value and burden of home-based work.

Beyond business as usual: integrated HIV care outside of the clinic walls

All TasP home testing-fieldworkers reported during the interviews that they were regularly asked by trial participants for additional services at home such as other HIV-related services (e.g. delivery of ART), sexual health services (e.g. pregnancy diagnosis, screening of sexually transmitted infections) and/or chronic care services, suggesting that home-based care could be an opportunity for the offer of a whole range of integrated services, beyond HIV, especially for poor and disadvantaged people. This result was corroborated by the quantitative study with a strong majority of participants supporting the introduction of a multi-diseases screening (86%) and ART initiation (85%) during home visits (Fig2).

> *"Many people who agree to be part of the [TasP] study are old people, grandmothers, grandfathers and aunts […] So if the government starts this programme of testing participants at home, it should also introduce blood pressure and diabetes [screening] so that it can also help old people." (FGD, TasP home testing-fieldworkers, participant 3)*

Moreover, many HCWs were in favour of pairing home-based services with community and clinic-based services. They repeatedly talked about the specificity of certain population groups who are responsive to certain delivery methods, at certain moments, in certain contexts; suggesting that a panel of HIV services would allow for a better response to the diversity of healthcare needs. HCWs explained how community-based services would be particularly adequate in this rural area, for HIV testing and support for linkage and retention in care: provided in tents or mobile clinics, strategically located in crowded community places like schools or community halls, possibly during social events such as sport tournaments, stage plays or on the days of national grants retrieval. Within the quantitative study, 71% of the participants agreed that HIV testing in mobile units would be acceptable by the population they serve (Fig2).

> *"What can assist in attracting the youth to test is to test them in mobile units, in sports-grounds and in places where there are events. If you find them in a sports-ground or anywhere where they can come with their friends, [then they can] test without everyone from home." (FGD, home-testing fieldworkers, participant 5)*

> *"The school children do not want to come [in the clinics for HIV testing]. If maybe there could be teams who visit schools [to offer HIV testing], just as X (referring to a government clinic situated in the trial area) did. X contributed a lot because it tested children at school." (SSI, government clinic nurse 3)*

Overall, HCWs were in favour of moving HIV care outside the clinic walls while pairing it up with other health services, tailored to address the national burden of disease.

DISCUSSION

This study explored, in the context of a large-scale community-based trial conducted in rural South Africa, the views of HCWs towards HIV services delivered at people's home: HIV testing, support for linkage to HIV care, and support for retention in HIV care. Our findings overall highlight that, regardless of whether they themselves delivered HIV services to people's homes, or whether they reported positive or negative field experiences, all HCWs considered the delivery of services at home as feasible and acceptable by the population they serve. Similar findings were noted in quantitative and qualitative studies examining home-based HIV services delivery in sub-Saharan Africa [40-43]. HCWs thus supported home-based services as one of the key components of a comprehensive UTT strategy to benefit people's health.

Our results demonstrated that home-based HIV testing plays a key role in ensuring high HIV testing coverage within rural communities, especially in underserved areas. This positive qualitative assessment of the HIV testing services is supported by the trial quantitative results, as the vast majority of the trial population (92%) accepted to be tested for HIV at home [31]. Such analysis is confirmed by other quantitative [40, 43-45] and qualitative studies [46] that examined the impact of home-based testing on HIV testing coverage in sub-Saharan Africa. HCWs also underlined that testing people at home provide opportunities to identify people living with HIV early in their infection, supporting its potential to assist a UTT strategy: the earlier a person gets to know about his/her status, the sooner he/she can be introduced to ART, and subsequently improve his/her own health and prevent the transmission of the HIV infection. Besides, a growing literature on cost-effectiveness of home-based services including HIV testing, outline the relevance of moving outside of the clinic walls to improve people's health [47]. These findings are in line with the UNAIDS targets, outlining the importance of increasing the number of people who are aware of their HIV status.

HCWs highlighted the positive influence home visits have on increasing access to HIV care in the community, regardless of the type of services delivered. HCWs have shown potential to assist people in navigating the HIV care trajectory from their home to the clinic [46, 48]. Our analysis thus confirms the capacity of home-based services to encourage people to seek healthcare, while reducing the burden on the facility-based health system. Those results are supported by previous quantitative and qualitative analysis in the TasP trial that show that home

visits for HIV testing and support for linkage and retention in care participate in encouraging people to initiate ART early [49, 50]. Such findings are complemented by those of other studies in sub-Saharan Africa that make apparent the key role of home-based services in improving and sustaining ART initiation and adherence [44, 51-53].

However, some of the disadvantages of home-based services were revealed by our findings. Some population groups are left behind by home-based services, including young adults and men [11, 43, 54]. Further research is required to adapt home services to such vulnerable populations. Respondents also outlined that home-based services should rather be implemented as complements to the existing facility and community-based services, rather than as standalone strategies. Such findings build on the plea for differentiated and person-centred care to reach the UNAIDS targets, especially in resource-constrained settings with high burdens of HIV infection [55].

Our study reports on several of the specificities of providing health services outside of health centres, in people's homes. First, respondents described the underlying fear of status disclosure and stigma happening within households. As initiation and maintenance of people's HIV care trajectories have been shown to be influenced by family support [56-58], our study confirms the key role of a caring steady family environment in the success of one's home-based care. HCWs therefore stand in favour of safeguarding confidentiality and preventing possible coercion, discrimination and other adverse consequences for populations being offered services in their homes. Second, HCWs reported on the specificities of provider-patient interactions at people's homes, mainly related to the nature of home-based HIV services. Such findings add up to those of other studies, noting that HCWs engaged in extended one-to-one talks outside of the comfort-zone of a clinic, and formed professional and social relationships with their patients [59-63]. Such a privileged relationship could inspire action in people and provide them with support to take up and maintain access to HIV services.

HCWs reported on the demands emerging from community members, and themselves argued, that home-based approaches for HIV care could be leveraged as a conduit for delivering care beyond testing and support. Such findings support ART initiation, delivery and monitoring at people's homes, which have been shown to be feasible and acceptable in sub-Saharan African countries [52, 53, 64] and are currently being considered as promising innovations in South Africa [28] and other high-prevalence settings [65]. In response to the national burden of disease, the use of home-based approaches to address other long-term conditions beyond HIV has also been widely encouraged by community members. Such a stance is supported by the

recent multi-diseases home-based interventions which have been investigated in sub-Saharan Africa, with great success in terms of acceptability [66, 67] and indications of likely cost-effectiveness [18, 68], and which are also in the pipeline of national health strategies, including in South Africa [28]. With the international focus on Universal Health Coverage [69, 70], home-based interventions seem attractive to reshape the disease specific and care-oriented services towards more comprehensive goals [71, 72]. But the features of such an integrated health system approach remain to be defined, including the careful selection of the services to benefit the health of family members and not overburden them unnecessarily. Substantial organizational efforts are expected for the implementation of standardized and yet context-specific solutions [73, 74].

Government HCWs, in addition to adopting a positive position for the scale up of home-based HIV services in the Hlabisa area, insist on the lessons learnt from the current local home-based care programme. They value the support provided by CCGs to the government clinics but note the poor supervision and irregular geographical distribution. Such findings support the formalizing of home-based care (Box 1) in line with the current efforts undertaken in several sub-Saharan African countries including in South Africa [28]. Government and TasP staff unite to plea for adequate training and support of HCWs (Box 1), adding to the growing claim of the health profession in sub-Saharan African countries for training opportunities that fully embrace the broad spectrum of competencies and cadres, in order to effectively meet health needs [75, 76]. Government and TasP staff also pointed out how an official recognition of the specific value and burden of their work could participate in improving the delivery of services in people's homes (Box 1), in keeping with the words of other HCWs who delivered home-based services, including HIV services in South Africa [77]. Those findings come at a time when the last decade has highlighted major gaps in the availability, accessibility and quality of the health workforce in many countries [78-80] and home-based HCWs represent an opportunity to shape the development of a new workforce and rationalize health care demands [81, 82]. Based on the insights of HCWs, we formulated pragmatic recommendations to policy-makers, to implement and improve the delivery of home-based services as a key component of national health systems (Box 1).

Box 1: Recommendations to implement and improve the delivery of HIV services at home, in rural areas: lessons learnt from HCWs

- Policy implementation: To formalize the delivery of home-based services
  - To mandate home-based services as part of HIV care, within all pertinent program guidelines
  - To develop practice standards at national, district and sub-district levels that are adapted to people's needs (home visits outside of working hours, phone calls prior home visits, mechanisms to transport people from home to clinics)
  - To drive policy-makers into understanding the distinctiveness of home-based work and challenge them to make long-term commitment to funding home-based programs
- Health services management: To build a home-based workforce
  - To recruit a specific workforce to be assigned to home visits
  - To integrate and articulate the workforce into the existing clinic-based pool staff
  - To provide the workforce with strong management and supervision, including allowing for feedback mechanisms
- Human resources: To adequately train and build the skills of the home-based workforce
  - To manage psychological aspects encountered during home visits (confidentiality, coercion, discrimination, especially with vulnerable population groups (e.g. men, young adults))
  - To build a cultural sensitivity to really get the value of home-based work through the building of privileged provider-patient interactions

One of the limitations of the quantitative part of the study was that questionnaires were written in English. This may have prevented the staff members who were less proficient in English from fully understanding the questions. Piloting the questionnaires prior the onset of data collection helped change the wording of some questions to minimize misunderstandings. One of the limitations of the qualitative part of the study is that participants may have responded in a way that they felt was expected as researchers who carried out the analysis were also working within the TasP trial. For some health care workers delivering home-based services in the TasP trial, this study allowed them to reflect on their own activity, which may have biased their response in one way or another. We noticed signs of irritability when they felt that the quality of their work was questioned and we assumed that they might have been reluctant to make critical responses. Additional training was given to the qualitative interviewers on probing to capture a full range of experiences. We ensured anonymity and created a space for open critical discussion, by open-ended questioning, and critical responses did emerge. Additionally, we aimed at an in-depth understanding of the context-specific issues through a close collaboration between isiZulu-speaking qualitative interviewers and researchers with an

extensive knowledge of the UTT strategy of the TasP trial. Finally, even though our study results may not be generalizable outside of the context of clinical trials and outside of South Africa, they bring valuable insights to understand the challenges of HIV service delivery in rural KwaZulu Natal, one of the most HIV-affected areas in the world; our results also provide informative lessons for contexts that are similar to our study setting (weak health systems serving particularly vulnerable populations living in dispersed settlements and greatly affected by HIV).

This study is, to our knowledge, the first investigating home-based services in the framework of a UTT strategy. The mixed-methods design allowed a comprehensive investigation process of the situation. By and large, many of the difficulties of formalizing and strengthening home-based care are currently being investigated. This paper seeks to place these challenges in the South African context, which is rapidly evolving with respect to changing health needs: all people living with HIV are now eligible for HIV treatment. Our analysis confirms that home-based HIV services hold a prominent place in the UTT arsenal to improve the overall care cascade. The central challenge appears to lie less in technical systems design than in making a case for a home-based system to be a part of the established health system.

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COMPETING INTERESTS

The authors declare that Merck & Co. Inc. and Gilead Sciences supplied the TasP trial with Atripla®. They declare that they have no further competing interests. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

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DATA AVAILABILITY STATEMENT

Raw data collected for this study contains potentially sensitive information for a small sample of participants and therefore cannot be publicly shared. Access to source data within an analysis matrix is provided as a supplementary information file (Supplementary file 1)

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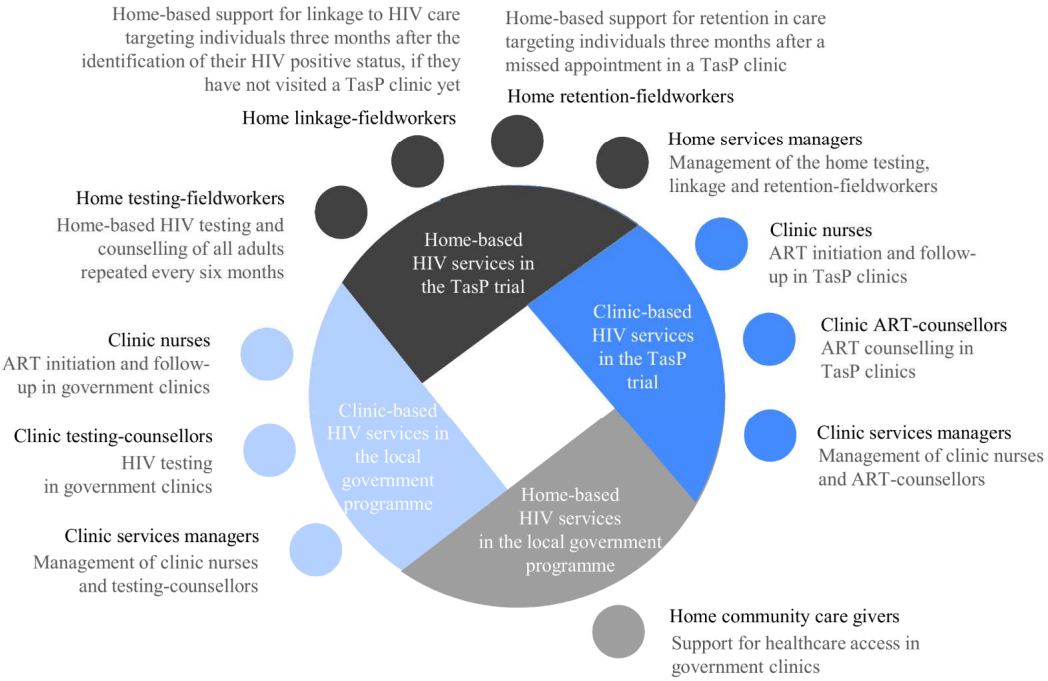


Fig1. Study population

ART: antiretroviral treatment, TasP: ANRS 12249 Treatment-as-Prevention trial

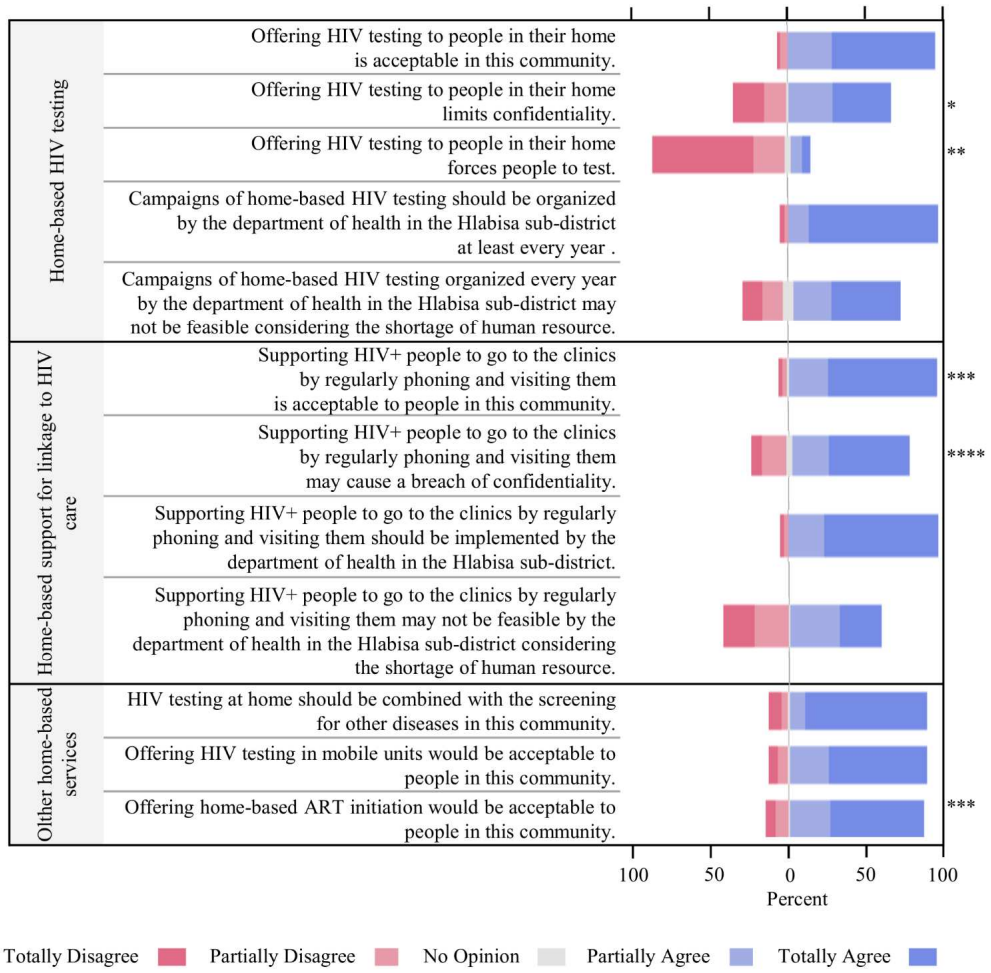


Fig2. Perceptions of HCWs on HIV services delivery (n= 146)

ART: antiretroviral treatment, * The variable has 2 missing values, ** The variable has 1 missing value, *** The variable has 3 missing values, **** The variable has 4 missing values.

Supplementary Table S1. Topics mentioned by health care workers during the qualitative study (ANRS 12249 TasP trial, Hlabisa sub-disctrict, South Africa, 2014)

	IDI - TasP Home linkage-fieldworker 1	IDI - TasP Home linkage-fieldworker 2	IDI - TasP Home retention-fieldworker	IDI - TasP Home services manager 1	IDI - TasP Home services manager 2	IDI - TasP Clinic nurse 1	IDI - TasP Clinic nurse 2	IDI - TasP Clinic nurse 3	IDI - TasP Clinic nurse 4	IDI - TasP Clinic ART counsellor 1	IDI - TasP Clinic ART counsellor 2	IDI - TasP Clinic trial manager 1	IDI - TasP Clinic trial manager 2	IDI - Government Clinic nurse 1	IDI - Government Clinic nurse 2	IDI - Government Clinic nurse 3	IDI - Government Clinic services manager 1	IDI - Government Clinic services manager 2	FGD – TasP Home testing-fieldworkers	FGD – TasP Clinic nurses	FGD – TasP Clinic ART counsellors
1 **Home-based services have the potential to draw into care people who have slipped through the cracks of the existing health care system**																					
1.1. Home-based services are perceived as highly acceptable and very convenient.																					
1.1.1. People appreciated receiving HIV services at home.	x	x									x								x		
1.1.2. Home-based services allowed to overcome common structural and individual barriers to facility-based health services.		x		x	x										x				x		
1.2. Home-based services enable a strong support for HIV care due to family closeness and connectedness with HCWs.																					
1.2.1. The family is central in people's acceptance of HIV services at home.	x		x																x		
1.2.2. HCWs display strong interpersonal skills to perform services at people's homes.	x	x		x	x														x		
1.3. Home-based services are conducive to promoting entry and retention in HIV care.																					
1.3.1. Home-based HIV testing allow people to learn about their positive HIV status early							x	x	x						x	x			x		x
1.3.2. Personalized support at home encourage people to enter and be retained in care.		x		x				x								x		x	x		x
1.3.3. Respectful HIV services at home contributed to building people's trust towards clinic-based health care.																x					

IDI: in-depth interview, FGD: focus group discussion

Supplementary Table S1 (ctd.). Topics mentioned by health care workers during the qualitative study (ANRS 12249 TasP trial, Hlabisa sub-disctrict, South Africa, 2014)

	IDI - TasP Home linkage-fieldworker 1	IDI - TasP Home linkage-fieldworker 2	IDI - TasP Home retention-fieldworker	IDI - TasP Home services manager 1	IDI - TasP Home services manager 2	IDI - TasP Clinic nurse 1	IDI - TasP Clinic nurse 2	IDI - TasP Clinic nurse 3	IDI - TasP Clinic nurse 4	IDI - TasP Clinic ART counsellor 1	IDI - TasP Clinic ART counsellor 2	IDI - TasP Clinic trial manager 1	IDI - TasP Clinic trial manager 2		IDI - Government Clinic nurse 1	IDI - Government Clinic nurse 2	IDI - Government Clinic nurse 3	IDI - Government Clinic services manager 1	IDI - Government Clinic services manager 2	FGD – TasP Home testing-fieldworkers	FGD – TasP Clinic nurses	FGD – TasP Clinic ART counsellors
2 Home-based services are not a magic bullet																						
2.1. Home-based services don't reach everyone																						
2.1.1. People were not present in their households at the time of the home visits.																				x		
2.1.2. Some people refused services.																				x		
2.2. Home-based services do not always preserve full confidentiality and freedom of choice.																						
2.2.1. People feared being seen in contact with an institution working on HIV.	x	x			x			x												x		
2.2.2. Unintentional HIV status disclosure could occur.	x																			x		
2.2.3. Possible coercion of people by their family members into accepting or refusing home-based HIV services.	x	x	x		x															x		
2.2.4. Possible coercion of people by HCWs into accepting home-based HIV services.																						x
2.3. Home-based services entail challenging working conditions.																						
2.3.1. HCWs are emotionally affected while assisting very poor and disadvantaged people.		x																		x		
2.3.2. HCWs experienced unpleasant, and even scary, situations while delivering services in the community	x	x																		x		
2.3.3. There is a lack of an established policy framework for home-based services in the current government services																			x			

IDI: in-depth interview, FGD: focus group discussion

Supplementary Table S1 (ctd.). Topics mentioned by health care workers during the qualitative study (ANRS 12249 TasP trial, Hlabisa sub-disctrict, South Africa, 2014)

	IDI - TasP Home linkage-fieldworker 1	IDI - TasP Home linkage-fieldworker 2	IDI - TasP Home retention-fieldworker	IDI - TasP Home services manager 1	IDI - TasP Home services manager 2	IDI - TasP Clinic nurse 1	IDI - TasP Clinic nurse 2	IDI - TasP Clinic nurse 3	IDI - TasP Clinic nurse 4	IDI - TasP Clinic ART counsellor 1	IDI - TasP Clinic ART counsellor 2	IDI - TasP Clinic trial manager 1	IDI - TasP Clinic trial manager 2	IDI - Government Clinic nurse 1	IDI - Government Clinic nurse 2	IDI - Government Clinic nurse 3	IDI - Government Clinic services manager 1	IDI - Government Clinic services manager 2	FGD – TasP Home testing-fieldworkers	FGD – TasP Clinic nurses	FGD – TasP Clinic ART counsellors
3 **Home-based HIV services promote re-thinking the current model of care towards differentiated care**																					
3.1. Support for the integration of home-based HIV services in the local health system, despite organizational challenges																					
3.1.1. Reasons to support the implementation of home-based services in the local model of care.	x	x	x	x	x											x		x	x		
3.1.2. Organizational challenges that would ensue from the integration of home-based HIV services in the local HIV programme.	x		x	x	x														x		x
3.1.3. Advice for implementers to implement home-based services at a large scale.	x	x	x			x	x	x		x		x	x	x	x	x	x			x	x
3.2. Beyond business as usual: integrated HIV care outside of the clinic walls																					
3.2.1. Possible additional services to be delivered at home	x	x	x	x													x		x		
3.2.2. Possible to pair home-based services with community and clinic-based services.				x	x														x		

IDI: in-depth interview, FGD: focus group discussion

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RESEARCH ARTICLE

Implementing universal HIV treatment in a high HIV prevalence and rural South African setting – Field experiences and recommendations of health care providers

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Abstract

Background

We aimed to describe the field experiences and recommendations of clinic-based health care providers (HCP) regarding the implementation of universal antiretroviral therapy (ART) in rural KwaZulu-Natal, South Africa.

Methods

In Hlabisa sub-district, the local HIV programme of the Department of Health (DoH) is decentralized in 18 clinics, where ART was offered at a CD4 count $\leq$500 cells/μL from January 2015 to September 2016. Within the ANRS 12249 TasP trial, implemented in part of the sub-district, universal ART (no eligibility criteria) was offered in 11 mobile clinics between March 2012 and June 2016. A cross-sectional qualitative survey was conducted in April–July 2016 among clinic-based nurses and counsellors providing HIV care in the DoH and TasP trial clinics. In total, 13 individual interviews and two focus groups discussions (including 6 and 7 participants) were conducted, audio-recorded, transcribed, and thematically analyzed.

Results

All HCPs reported an overall good experience of delivering ART early in the course of HIV infection, with most patients willing to initiate ART before being symptomatic. Yet, HCPs underlined that not feeling sick could challenge early ART initiation and adherence, and thus highlighted the need to take time for counselling as an important component to achieve universal ART. HCPs also foresaw logistical challenges of universal ART, and were especially concerned about increasing workload and ART shortage. HCPs finally recommended the

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need to strengthen the existing model of care to facilitate access to ART, e.g., community-based and integrated HIV services.

Conclusions

The provision of universal ART is feasible and acceptable according to HCPs in this rural South-African area. However their experiences suggest that universal ART, and more generally the 90-90-90 UNAIDS targets, will be difficult to achieve without the implementation of new models of health service delivery.

Introduction

It is well known that health care providers (HCP) are key actors in the effectiveness of health services, especially regarding HIV care [1, 2]. They are in particular responsible for the technical quality of care (services must be performed according to pre-defined medical standards) and the service quality (how services respond to patients' expectations and cultural values) [3]. In the fight against HIV infection, HCPs have been in the front line for implementing the successive changes in antiretroviral therapy (ART) initiation eligibility criteria. ART was first recommended by the World Health Organisation (WHO) for HIV-infected patients with moderate and advanced stages of infection, at a CD4 count $\leq$200 cells/μL in 2002 [4] and a CD4 count $\leq$350 cells/μL in 2010 [5]. Then, in the last few years, initiating ART earlier in the course of HIV infection was shown to significantly decrease the risk of HIV-related morbidity and mortality [6, 7] and of HIV transmission within serodiscordant couples [8]. As a consequence, the WHO progressively updated its guidelines with ART initiation recommended at a CD4 count $\leq$500 cells/μL in 2013 [9] and regardless of clinical or immunological stage (i.e. universal ART) in September 2015 [10], as part of the Universal Test and Treat (UTT) strategy [11].

The beliefs, attitudes and experience of experts and HIV specialists towards universal ART have been documented in high-income countries [12–16] where universal access to ART has been available even prior the launch of the 2015 WHO guidelines. Interviewees had good perceptions of the efficacy of universal ART but highlighted the importance of considering patients on a case by case basis, deciding on the best time for ART initiation according to their individual characteristics, related to lifestyle, social support, travels. In sub-Saharan Africa, which carries the greatest burden of HIV, research on access to and delivery of universal ART has mainly been focused on patient perspective, including the investigation of individual and social barriers to HIV care [17, 18]. The perspective of HCPs regarding successes and barriers of offering ART to people early in the course of their HIV infection has not yet been documented, even if it has been identified as essential to inform policy makers in designing service delivery models that are acceptable, efficient and sustainable for the scale up of universal ART [19].

In South Africa, HCPs have provided ART at a CD4 count $\leq$500 cells/μL in the Department of Health (DoH) HIV programmes since January 2015 [20]. Universal ART was delivered on an experimental basis between 2012 and 2016 within the ANRS 12249 TasP (Treatment as Prevention) trial conducted in KwaZulu-Natal province [21]. As other sub-Saharan countries [22], South Africa has adopted in 2016 the WHO guidelines recommending universal ART as national policy [23]. The number of people on treatment is thus likely to increase from 5.4 million to 7.4 million in 2020 countrywide according to modelling studies [24, 25]. Ensuring that all people living with HIV are able to start ART early in the course of their infection and

receive it for life in good conditions will probably be a major challenge for the South African health system overall, and especially for HCPs. The objective of this study is to describe and compare the field experiences and recommendations of clinic-based HCPs working in both the DoH and in the TasP trial clinics regarding the early implementation of universal ART in rural KwaZulu-Natal, South Africa.

Materials and methods

Study setting

This study was conducted within Hlabisa sub-district, a rural area of the KwaZulu-Natal province in South Africa, where an estimated 29% of the adults aged 15–49 were HIV-positive in 2012 [26]. The Hlabisa local DoH HIV programme was initiated mid-2004 [27]. It is devolved to 18 primary health care clinics in the sub-district, and is nurse-led, with certain nurses trained for Nurse-Initiated and Managed Antiretroviral Treatment (NIMART) programme since 2011. People can access HIV testing and counselling at any time in these government clinics and receive ART for free if they are eligible, according to the South African national guidelines as follows: at a CD4 count $\leq$350 cells/μL prior January 2015, then at a CD4 count $\leq$500 cells/μL until September 2016 when universal ART (no specific criteria for ART initiation) was adopted countrywide.

Between March 2012 and June 2016, the cluster-randomised ANRS 12249 TasP trial was implemented in part of Hlabisa sub-district, under the responsibility of the Africa Health Research Institute (AHRI). This trial aimed to compare the effect of universal ART, initiated in all adults living with HIV regardless of clinical or immunological stage (intervention arm), versus ART initiated according to South African guidelines (control arm), on the reduction in incidence of new HIV infections in the general population [21, 26]. All individuals, aged $\geq$16 years, reporting being a member of a household of the 22 trial cluster areas, were eligible to participate in the trial. They were offered HIV testing at home every 6 months by fieldworkers; those identified HIV-positive were referred to a cluster-based clinic, set-up especially during the trial period, nurse- and counsellor-led, situated <45 minutes walking from where they lived.

Study design, study population and sample

A cross-sectional mixed-method survey was conducted among HCPs from both the DoH programme and the TasP trial to investigate their experience in providing early and universal ART, and their perception of the scale-up of UTT [28]. The quantitative component was conducted in April 2016; all TasP and DoH HCP were invited to participate. In this paper, we focus on the qualitative component of the survey, which was conducted in May-July 2016 and consisted of semi-structured individual interviews (IDI) and focus-group discussions (FGD). TasP and DoH HCPs were selected among the staff met during the quantitative component of the study, and based on three main criteria (age, years of experience, high versus low clinic volume) in order to capture diverse professional contexts. Here, the analyses focused on data collected among clinic-based staff, including eight IDIs in TasP (two nurse managers, four nurses and two ART counsellors), five IDIs in the DoH (two government clinic managers and three ART nurses). Two FGDs were also conducted with seven nurses and six ART counsellors, all members of the TasP team (Table 1).

Data collection

Four local experienced qualitative interviewers carried out the IDIs and FGDs in isiZulu. IDIs lasted for 60 to 90 minutes in English or isiZulu and the FGDs for about 120 minutes in

Table 1. Study population and sample–Hlabisa sub-district, South Africa, 2016.

		Total population (enrolled in the quantitative component)*	Qualitative study sample	Sample characteristics			
				Interviewee	Gender	Age	Years of experience in HIV care
HCPs eligible for the quantitative component							
TasP	Clinic-based managers	3 (all enrolled)	2 IDIs	IDI TasP Nurse Manager 01	F	44	11
				IDI TasP Nurse Manager 02	F	39	8
TasP	Nurses	19 (15 enrolled)	4 IDIs	IDI TasP Nurse 01	F	35	8
				IDI TasP Nurse 02	F	53	8
				IDI TasP Nurse 03	F	34	6
				IDI TasP Nurse 04	F	71	10
			1 FGD with seven participants	FGD TasP Nurse, P1	M	28	6
				FGD TasP Nurse, P2	F	72	9
				FGD TasP Nurse, P3	F	71	8
				FGD TasP Nurse, P4	F	34	8
				FGD TasP Nurse, P5	F	53	9
				FGD TasP Nurse, P6	F	35	5
				FGD TasP Nurse, P7	F	28	5
TasP	ART counsellors	15 (all enrolled)	2 IDIs	IDI TasP Counsellor 01	F	46	16
				IDI TasP Counsellor 02	F	31	9
			1 FGD with six participants	FGD TasP Counsellor, P1	F	58	13
				FGD TasP Counsellor, P2	F	32	6
				FGD TasP Counsellor, P3	F	58	14
				FGD TasP Counsellor, P4	M	29	6
				FGD TasP Counsellor, P5	F	54	14
				FGD TasP Counsellor, P6	F	37	13
DoH	ART nurses	51 (40 enrolled)	3 IDIs	IDI DoH Nurse 01	F	47	17
				IDI DoH Nurse 02	F	63	7
				IDI DoH Nurse 03	F	50	6
Other HCPs							
DoH	Government clinic managers	18**	2 IDIs	IDI DoH Gov. Clinic Manager 01	F	31	3
				IDI DoH Gov. Clinic Manager 02	F	56	17

HCP: health care providers; IDI: individual interview; FGD: focus-group discussion;

TasP: Treatment as Prevention trial; DoH: Department of Health; ART: antiretroviral therapy

F: Female; M: Male; P: Participant

* Total number of HCPs per category at the time of beginning the study in April 2016 (in brackets, number of HCPs enrolled in the quantitative component)

** DoH government clinic managers were not targeted by the quantitative component of the survey

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isiZulu. They were held either in a closed meeting room at AHRI (for the TasP staff) or at a place of convenience including within the clinics (for the DoH participants). Structured guides

were used for IDIs and FGDs. Each guide was specific to the job position and addressed experiences in providing early ART (DoH) and universal ART (TasP), perceptions regarding the scale-up of universal ART, and perceptions regarding HIV services to increase access to HIV care and treatment. The FGDs and IDIs were audio-taped. Transcription of recordings and translation from isiZulu to English were performed by the interviewers themselves, and all translations were validated independently by the qualitative survey supervisor.

Analysis process

An inductive approach based on descriptive thematic coding was used. All transcripts were entered into qualitative data analysis software (NVivo version 11, QSR International Pty Ltd., Doncaster, Victoria, 3108, Australia). Codebooks were developed using an iterative process: initial codes matched the predefined research themes (working conditions; attitudes of community members regarding HIV services; future of HIV services), then were expanded with codes reflecting the participants' own terms and semantics, and discussed within the team, including qualitative interviewers and researchers, for triangulated input.

Ethics

The study was approved by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal on 18 March 2016. All participants voluntarily provided informed written consent.

Results

Description of the study sample

Of the 88 HCPs registered as DoH and TasP staff members in April 2016 and eligible to the quantitative component, 73 participated (15 were not present in the clinics; no refusal was recorded). Among them, 24 study participants were purposively selected to participate in the qualitative component; in addition, two DoH government clinic managers were recruited. Overall, 26 participants (24 women and two men) were included; their socio-demographic characteristics are presented Table 1. Briefly, HCPs were between 28 and 71 years old, with a median of 45 years. They had between 5 and 17 years of experience in providing HIV care.

HCPs are motivated to provide universal ART, which contributes to better health and better care for people living with HIV

Early/Universal ART revitalized the community. All TasP and DoH HCPs appreciated initiating people on ART early in the course of the HIV infection (CD4 $\leq$500 cells/μL in the DoH and regardless of any criteria in the TasP trial), feeling that they were saving people's lives, participating in reducing their patients' risk of developing opportunistic infections. HCPs also noted that, beyond individual benefits, early ART had positively impacted on the community. As a consequence of more and more people initiating ART early, they perceived, among the community, increasing confidence and hope in the health system to improve people's health and fight HIV infection.

> "We initiate people [on ART] while they are still fine, so the benefits [of early ART] were helpful. We managed to revive the community [. . .] I think initiating ART early before people become sick, regardless of their CD4 count, has helped the Hlabisa community. Because it wouldn't be right to find that a whole family is sick, that all die at the same time, and no one is left to take care of the children." (IDI TasP Nurse 03)

"It has been a while since I last saw a person being transported in a wheel barrow. It means people have hope. They are able to make decisions in time. It is rare to now find a person being bedridden in his/her homesteads. It means that there really is hope, and that we will win this fight." (IDI TasP Counsellor 02)

Early/Universal ART encourages people to seek care. Both TasP and DoH HCPs emphasized that the absence of HIV-related symptoms associated with early ART was a major motivation factor for people to initiate ART as soon as possible, as it contributed to preserve them from HIV-related stigmatization and discrimination from community members.

"[Some patients] approve it (referring to universal ART) as they don't want to have the symptoms which make it obvious to others that they are HIV positive: symptoms like TB, weight loss and shingles. They like the fact that they recover sooner than the next person noticing that they do not suffer from opportunistic disease. They do not suffer from diarrhoea. People appreciate early ART initiation as other people won't see those on ART having symptoms." (IDI TasP Nurse 04)

"If you tell [the patient] that their CD4 count is this much, they would say [. . .] 'wow it so high!' [. . .]. The patient appreciates it because you have already taught them that it helps them to not get sick. And so they will not to not be seen [as sick] by people [. . .]. [When] you tell the patient about all the benefits [of initiating ART early], they really like that. Firstly they get surprised by their [high] CD4 count, then, once they know that they will be offered ART [regardless of the high CD4 count], that give them hope." (IDI TasP Counsellor 01)

Additionally, HCPs witnessed a positive snowball effect of early ART in the communities. Visible health benefits of early ART were encouraging some of those who had been indecisive or reluctant about starting ART, to take action and seek HIV care.

"People who started [early ART] were pioneers into attending the clinics. As others started seeing them getting better, it helped them to feel free to come to the clinics [as well]." (IDI TasP Nurse Manager 01)

Early/Universal ART allows for improvements of health care delivery. Both TasP and DoH HCPs appreciated the flexibility in their HIV care practice when dealing with people with higher CD4 counts, who were not urgently in need of ART. They explained that offering ART at high CD4 counts facilitated the relation between HCPs and their patients as asymptomatic people had better capacities of concentration and of understanding the counselling provided compared to the sickest ones. They also enjoyed being able to take time (i.e. several days) to offer more in-depth counselling for these patients and thus better organize their work schedule without rushing for ART initiation.

"It (referring to the change of ART eligibility from CD4 count $\leq$350 to $\leq$500 cells/μL) did make a change in [managing] patients, because now we initiate people who are still able to walk around, who are not in bed. It is different from before, when we were initiating people that were emaciated and very weak; it was not easy for them to regain weight and it was taking long. But now it's easier because the patient is able to walk, is able to answer to all the questions we are asking him/her. It is unlike when the person was very ill and we needed a relative to talk to [. . .] because if the person is too ill, he/she is unable to understand [what

we are saying], they are only able to concentrate on their illness [. . .]. [With ART eligibility at 500 CD4 cells/μL], the [patient] queue goes fast." (IDI DoH Nurse 02)

"With this type of participants [in immediate need of ART], I first need to make them understand that they need to start treatment and that they must come [back to the clinic] the following day [to start treatment]. That participant doesn't have enough time to understand the situation because I have other duties that I have to do. But I do talk with them and tell them the importance of starting treatment and so on. It is different with participants with who I can have time with [because they have high CD4 count and are therefore not in immediate need of ART]. I can plan their appointment only for counselling [. . .]. Such person [who starts ART at high CD4 count] has time to get detailed information [about ART] as compared to the person who has a low CD4 count [and is in immediate need of ART." (FGD TasP nurses, P1)

In addition, some HCPs also suggested that the implementation of universal ART could contribute to decrease the burden on the health system, especially related to patients not yet eligible for ART and who were at risk of presenting to the clinic with advanced disease thus requiring hospitalizations.

"I think it (referring to universal ART) can reduce the burden on health care professionals. There are lot of people that are tested HIV positive but because their CD count was above 500 (eligibility criteria for ART initiation at the time of the interview), they would go home and forget about coming back to initiate treatment. [Universal ART] can reduce the number of people we see coming in stretchers and at times they are in Stage 3 and 4. [. . .] This will reduce the number of people who end up being hospitalised as they eventually become severely ill. On the other side this will enslave us. (Laughing). [. . .] we will end up working hard to achieve the target."(IDI DoH Gov. Clinic Manager 01)

HCPs perceive challenges in providing universal ART to reluctant patients and without sufficient human resources and equipment

Early/Universal ART is offered to people who can be reluctant to initiate ART. Both TasP and DoH HCPs reported that some of their patients were not aware of the rapid changes in the ART landscape and eligibility criteria. Because they lacked knowledge about the evolution of HIV medicine, the benefits of prompt ART initiation upon diagnosis as well as the availability of pills with less side effects than before, those patients were reluctant to initiate ART early in the course of their HIV infection.

"Some [patients] were looking in the past; there were many bad side effects before. Like when people were taking D4T (referring to the ART drug stavudine which has been commonly used in South Africa before 2011), they body structures were changing. So now, they have that fear that if they start taking treatment, they will have big legs or big breasts. That was becoming a concern to them. So your role is to tell them that we know that and we have addressed it. Most of the pills that were causing those problems have been removed." (FGD TasP Nurses, P3)

Both TasP and DoH HCPs also underlined that they faced specific difficulties in encouraging people with high CD4 count, and especially no HIV-related symptoms, to initiate ART. They acknowledged that HIV disease acceptation could be a long process for those individuals. They were concerned about the fact that some of their patients, and especially the youngest

ones, might not see the value of HIV care and ART initiation early in the course of their HIV infection. Some patients feared to engage in taking ART for life. HCPs also noted that some of their patients feared that ART side-effects would make them look sicker than how they truly felt.

> "Those who are younger, they see themselves as healthier than others. They look at those with a low CD4 count, saying: 'oh! I will not go to clinic while I am severely sick and people are holding me'. You see that attitude. [. . .] I feel sad because those persons will end up getting sick. They will decide to start ART only when they are severely sick. Because ART is very strong, the patients may think that it is because of the treatment that is why they are getting worse. I explain to the patients, and ask them to come back so that we can talk." (IDI TasP Nurse 02)

In this context, HCPs consensually agreed on the key role of counselling to answer the expectations of their new patients, starting from their first clinic visit: allowing them time to claim ownership on the decision of initiating ART early during their infection, and finding the right arguments to make the risk/benefits balance tip in favour of early ART initiation.

> "It happens [that people hesitate to initiate early ART], but it's because of fear of unknown and because when HIV came it came with fear. Some become hesitant saying I will start the treatment and be like my neighbour who is not right and sick [. . .] I don't feel right but there are skills such as counselling them so they end up leaving with different attitude, knowing the correct way [. . .] they [the patients] respond well on counselling when you talk to them you realise that they just lacked information, they did not know. Once you sit them down and talk to them and tell them how HIV works you notice they now understand and they will say nurse I now know and I'm prepared to do this" (IDI TasP Nurse 03)

Early/Universal ART is offered to people who may be more likely to default. Both TasP and DoH HCPs reported overall high ART adherence and retention in HIV care among their patients. However, they also emphasized how having high CD4 count and not feeling sick could compromise HIV disclosure, and thus challenge ART adherence. Based on their experience, some TasP HCPs were further worried that early ART initiation, among people who never felt sick, could lead some of them to forget the treatment benefits, or to not consider their health as a priority, which could result in treatment interruption, and ultimately emergence of ART resistance and complexification of HIV care management.

> "The dangers of early ART initiation is that, after some time, people stop taking ART. If they start treatment without ever being ill, they default and then develop resistance. You cannot guarantee that that these people will adhere to their treatment and not get tired of taking the treatment. They can say 'I have never been ill, I am now tired of this treatment'. When people default and start taking treatment again, they develop resistance [to their ART regimen]. And then we will have a lot of regimen 2, and we do not like that." (IDI TasP Nurse 03)

> "If they [referring to people with high CD4 count] start their treatment early, it can cause them not to adhere because they see they are healthy. They think that they can move to other places like Durban or Gauteng, and that they can even stop taking their treatment. Some will come back [to the clinics] when they are really sick. Good adherence is more found in people who started treatment when their CD4 count was low, when they really

needed to take treatment, than in those who have a high CD4 count, who have never been sick and for who it is really easy to dropout from taking treatment. They would just say 'I was not around for two weeks, my ARVs were finished'." (FGD TasP Nurses, P2)

HCPs again identified personalized quality counselling as a cornerstone for the success of ART adherence among people initiating early: discussing disclosure to trigger sustainable personal support and regularly reminding the role of ART in maintaining one's high health status.

"Counselling is a continuous thing. You don't do it in one day. In a sense that even with a participant who is taking treatment, it's a day to day counselling. Even if his/her adherence is good, you encourage him/her differently. Even that participant needs a counselling that is directed to him/her and according to his/her behaviour." (FGD TasP Nurses, P2)

Early/Universal ART could suffer from human resources and equipment shortage. All HCPs were in favour of making universal ART available in the area that they serve. Nevertheless, most of them pointed out several foreseen programmatic challenges of large-scale implementation of universal ART. As universal ART implies an increased patient volume receiving care, HCPs feared a decline in the quality of care in the local government clinics, in the absence of adequate efforts from the health care management in terms of human resources and health equipment. HCPs were concerned about clinic staff experiencing too much workload and wearing themselves out. And about patients suffering from longer waiting queues, receiving less individualized counselling, facing drug shortages and delayed lab tests results, and thus loosing motivation for HIV care and treatment. HCP overall highlighted the risks of quality deterioration and lessening of trust in both the HCP-patient and the HCP-health care management relationships.

"Even if [DoH staff] can be ready [to implement universal ART], the staff shortage will hinder their readiness. [. . .] A nurse can't work well when over loaded and it compromises the quality of care. [. . .] You would end up just dishing the medication [. . .] and missing a lot in the process. You would end up missing a person with unsuppressed viral load, [. . .] or with abnormal blood results or missing the normal health education. You would end up focusing on the [patient's] queue in the bench, and realize that you have so many patients to attend." (IDI TasP Nurse Manager 02)

"The concept [of universal ART] is good. The problem is: will it be sustainable? Hum. . . we have seen periods in the Hlabisa district, when [clinics] run short of treatment [. . .]. Then, patients are like yoyos. They will be on treatment, but what about the following day? They will not be. Because of ordering, or they have changed tenders. I think that is the frustrating part when it comes to treatment." (IDI TasP Nurse Manager 01)

"Shortage of treatment makes me sick. Because when patients start taking treatment, we tell them that: 'Don't forget it. Don't miss the pill'. So if there is no treatment [that we can give them], how can the patients trust us? How can they believe that they will survive if there are days when they do not take their treatment?" (IDI DoH Nurse 03)

HCPs suggest opportunities for successful scale up of universal ART

All HCPs were in favour of scaling-up universal ART in the government clinics of the area that they serve, while emphasizing that a successful implementation would require the healthcare management to command drastic changes in the current health system.

Efforts in constituting a wide and efficient workforce. First, HCPs urged health care management to adequately match human resources needs to promote quality health care and optimize patient management. They also advised on acknowledging the specific challenges of universal ART delivery and acceptability, therefore adequately training the nursing workforce to provide an adequate and personalized counselling to their patients.

> "[Providing] HIV care [to someone] is like caring [for any other] person. When they come to the clinic, you should be able to attend to all their needs, not only issuing them HIV treatment. Everything, including the social aspects [of HIV care]. [. . .] So if the work load is increased (with the implementation of universal ART), I don't think the nurses will be able to attend to the social needs [of their patients]. They will only focus on the queue, and just issue [people] tablets without knowing other problems the patients may also have." (IDI TasP Nurse 03)

Efforts in offering a diversity of ART supply strategies. HCPs suggested that several ART supply strategies could support a successful large-scale universal ART programme. They referred to services that they either knew of, experienced or witnessed in their work environment.

First, they advised on driving health facilities to be more flexible in providing ART to their patients: in opening clinics on Saturdays and systematically offering 3 months refill for stable patients (i.e. who are virally suppressed) in order to reduce the number of required ART pick-up visits and decrease the risk of non-adherence. Some DoH HCPs also experienced allowing community members (e.g. community caregivers (CCGs), directly-observed therapy (DOT) supporters, relatives) to pick up the drugs on behalf of patients, and such initiative was appreciated by community members who had difficulties to access the clinics to take their treatment.

> "People that give us difficulties [in ensuring they keep adhering to ART] are those who work in far areas, such as truck drivers. [. . .] But since we have started this new system of giving them three months of treatment, I think it's getting better now because they won't run out of treatment. We also give them a chance of sending their relatives to collect treatment for them, if their CD4 count remains controlled [. . .] And when they are back from work they can come anytime for check-up. We tell them to keep the date for blood taking, and for all other tests to come at least once a year." (IDI DoH Nurse 02)

> "Yah, there is a change right now it (referring to workload) has decreased again because of the chronic clubs; it is a programme for patients that are viral load suppressed and who adhere very well to their treatment. I've been taking to the fields where people are being given treatment by the CCGs. [. . .] The patients are happy about with the change because sometimes they do not have money to come here so to collect their treatment. So it helps a lot for the CCGs to collect their treatment as they only come sometimes twice a year for review of their bloods." (IDI DoH Gov. Clinic Manager 02)

Then, both TasP and DoH HCPs highlighted the importance of offering a combination of HIV care services, including ART delivery for stable patients, with the implementation of community-based services in addition to the health facilities. Moving beyond the clinic walls, directly in the community or in people's home, could indeed facilitate access to HIV care and treatment for older people, or those who live far from the clinic and/or who can't afford transportation costs.

"They are a few old women and men [who attend clinics for HIV care] [. . .] If people could be tested [for HIV] at home and be given ART at home, this would decrease the number of people on ART who default. Taking a taxi to go to the clinic is expensive [. . .]. If it could be known that on this day, we (referring to HIV HCPs) are visiting these people, they would then get their medications. That will ensure that no government funds will be wasted when people get sick because they default and therefore need serious medical care from the hospital, which costs money." (IDI TasP Counsellor 01)

Finally, TasP HCPs reported positive experiences in using phone calls and small text messaging (SMS) to encourage people identified HIV-positive within the trial in going to the clinics for ART initiation and follow-up. But one nurse questioned the ability of the DoH health system to implement such strategy, considering the nigh number of patients to contact.

"Another thing that I liked [in the TasP trial], even though it was a bit of work, is that we were following our participants. For example, if you find that if a participant is no longer coming to the clinic [for HIV care], you know that you have his/her phone number, then you can call him/her. Or you can track [at home] the participant with all this TasP staff (referring to the dedicated workforce who visited people's home to encourage them to initiate or adhere to ART). But I am not sure if the government can be able to use that system because he will have a huge number of participants." (FGD TasP Nurses, P6)

Efforts in integrating universal ART in a more comprehensive approach. Both TasP and DoH HCPs highlighted that ART initiation, especially among people with high CD4 count, could be positively influenced by the provision of HIV and ART information prior to clinic visit (including information on universal ART). They acknowledged how community mobilization, such as community-awareness campaigns (i.e. roadshows, as implemented within the TasP trial), or media mobilization (through TV or radios), could help to increase HIV and ART education as well as change cultural beliefs in the community. TasP staff also underlined the value of home-based HIV counselling and testing with fieldworkers who provided first HIV counselling.

"The challenge that they (referring to the DoH nurses) might face [in implementing universal ART in their clinics] are people's cultural believes, [fear of] stigma and [HIV status] denial. I will encourage them (referring to DoH staff) to focus on awareness as people do not change because they do not have the information. People do not understand what is in them (referring to the HIV virus) or how does it affects them. [But,], if people have a clearer picture, they do comply. They (referring to the DoH staff) must also [. . .] work hand in hand with the leaders and heads in the area. If they strengthen those rapports, it will be easy for them to approach people". (IDI TasP Nurse Manager 02)

"Some people listen to media, read pamphlets. Then they come to us aware of what is going on. [. . .] This made it easy [for us to work], because when they come to us they already know most things." (IDI DoH Nurse 01)

"Another thing that makes it easy is if s/he was referred by a trained fieldworker, who has counselling, who provided enough counselling for one to decide to come to the clinic. That makes it easy. When you start counselling that person, you see that they know a lot already and they are committed to start with us" (FGD TasP Counsellors, P1)

Additionally, TasP and DoH HCPs also suggested that universal ART acceptability in the community would benefit from involving actors from the community in the programme implementation, for example during awareness campaigns. Trusted community leaders such as religious representatives and ward counsellors (officially elected heads in South Africa) could provide reassurance and guidance to community members regarding their HIV care pathway; some people living with HIV could also stand up as expert-patients to testify on their experience and act as role models for those who have uncertainties or doubt regarding HIV care.

> "I think there is a role that they (referring to community leaders) have to play [in the implementation of universal ART]. They should let the community know, they should preach the gospel that if you know that you are HIV-positive, you should. Community leaders should know why it is important that people who are HIV-positive should start taking treatment. [. . .] I think that traditional leaders, pastors, and councillors. And mothers. . .women who look after virgin girls. Also those who do home based care (referring to CCGs) because they are community members [. . .] People trust community members. They know that if certain people speak, they believe that they are not misleading them. [. . .] I think they can get more people, some will take it seriously. Even the teachers in schools can speak with children, and say that there is something like this (referring to HIV care). If you know someone at home, you have to tell him/her [to access HIV care]. It's important." (IDI TasP Nurse 01)

Efforts in rethinking transversally the overall health system. HCPs supported the government efforts to integrate HIV services as part of a comprehensive health package (South African model of an "IDEAL clinic" [29]), noting how this would benefit large-scale implementation of universal ART. They were in favour of moving away from a restricted number of nurses specifically caring for people living with HIV, to a nursing workforce who is fully capable of caring for HIV and ART initiation (NIMART-trained) and other diseases. They explained how such health system organization would increase confidentiality for patients accessing the clinics for their HIV infection.

> "You will see that this person doesn't come for regular check-ups for CD4 count. Maybe some reasons are a long waiting time that we have in clinics. The services are divided, like when you came to see me, after we are done I will refer you to ART department, where you will be taking viral load. I think that was the main problem. It's a long waiting time, joining another queue, and again join another queue to open a clinical chart, and taking of bloods. And another thing is stigma. That I am from this community, and the people from this community will see that I started at the main clinic. Now that I am referred to ART department that means I tested positive. Maybe these were the main things." (DoH Gov. clinic manager 01)

> "The government wants to end this thing of having people who are seeing inclusively. He wants [to implement] a service point for chronic diseases to offer all services to the participant at the same time. So there cannot be a situation where we see someone belongs to ART, separately from other chronic cases. |. . .] So every nurse should have NIMART. Therefore wherever a participant enters, s/he will find a nurse that will be able to help him/her even if s/he is ART. The nurse will check bloods, and see that it is important to do this, everything you see in a well-trained nurse to work under any conditions." (FGD TasP Nurse, P2)

According to HCPs, allowing all nurses to provide care for HIV and also for other diseases which are of concern to people living with HIV (e.g. diabetes, cardiovascular diseases) would participate in answering people's healthcare expectations.

Discussion

In this high HIV prevalence and rural South African setting, HCPs reported an overall good experience of delivering ART early in the course of HIV infection, both in the government clinics (ART at a CD4 count $\leq$500 cells/μL) and in the TasP trial (universal ART), with many similar experiences between the two settings. Benefits of enlarging ART use to individuals with high CD4 count for the sake of people' health were well understood by HCPs, who were glad to report saving people's life and giving hope to their patients, as also reported by HCPs from high-income countries [12, 13]. HCPs also liked providing counselling to people with high CD4 count who had more ability to concentrate and compared to the sickest ones. According to the HCPs, patients were overall willing to initiate ART before being symptomatic and being seen as sick, which has also been observed in a study conducted in Swaziland [30]. High rates of ART initiation were indeed observed among ART-naïve individuals accessing the TasP clinics [17, 31]. These positive results are encouraging for the scale-up of universal ART in South Africa and elsewhere.

Our results also showed how universal ART changed the perception of HIV treatment among HCPs and their patients. While HCPs used to ask themselves whether a patient was eligible or not to start treatment based on clinical data, they now needed to shift their mindset to better understand their patients' global characteristics and develop strategies to support them to start treatment. Offering ART early and systematically in the course of HIV infection indeed seemed sometimes challenging for HCPs, with patients who did not feel sick, who did not see HIV care as a priority or needed time to accept and disclose their HIV status and to be ready to engage in HIV care and treatment for life. Reluctance to initiate ART as early as possible was also recently observed in Uganda among high-risk women who were offered universal ART [32]. While HCPs are convinced of the benefits of early ART initiation, they underlined the importance of not forcing people with high CD4 count to initiate ART immediately in order to avoid defaulting and thus offer individualized holistic care [12, 16]. In this context, universal ART thus emphasizes HCPs' responsibilities in terms of HIV counselling and ART education that should be offered at the first clinic visit but also continuously, and should be adapted according to patients' needs and behaviors [33]. HCPs especially need to take time to specifically explain the benefits of early ART initiation to their patients who might not be informed of the rapid changes of ART guidelines. HCPs also underlined the need for social support from the family and more generally from the community to increase early access to HIV care and treatment. People with high CD4 count may be particularly motivated to access HIV care seeing other community members being fine while on ART. The involvement of peers as well as community and traditional leaders have also been identified as opportunities to increase HIV awareness within the community and encourage people, especially the men and the youngest individuals, to access clinics and receive HIV care and treatment early in the course of their HIV infection [18].

Furthermore, our results highlighted the need to strengthen existing models of HIV care for the scale-up of universal ART and especially the clinical management of the patients. HCPs interviewed in our study foresaw an increase of people in clinics with the implementation of universal ART, as also suggested by modelling studies [24, 25]. They thus claimed for more human resources, especially NIMART nurses with counselling skills, to be employed to ensure good quality of care [34]. HCPs also underlined the importance of ensuring the availability of

drugs in order to avoid ART shortage. HCPs also emphasized that the implementation of universal ART will require substantial efforts to guarantee effective monitoring of people on ART and rapidly detect defaulters, which is key to inform differentiated care and maintain community viral suppression. Yet, while routine viral load testing is essential to detect early signs of ART adherence problems before immunological decline [35], and is now recommended as a standard of care for monitoring [36], such technology is not yet always available. This is not necessarily the case in South Africa but holds in many low and middle income countries [37].

Our results underlined that universal ART is not just giving drugs, but is also an opportunity to rethink the health care system organization. The experiences and perceptions of HCPs highlighted that, without proper support for linkage and for retention, universal ART was unlikely to succeed. While several strategies are known to be effective to increase access to HIV care, they have not routinely been implemented yet in our study setting, one of the most affected by HIV. HCPs thus provided valuable insights as to the state of implementation of these key strategies which could and should be rapidly scaled-up. First, HCPs argued for the delivery of HIV care combining both facility-based and community-based services, aiming at bringing health services closer to where people live or work, and aiming at addressing several barriers to HIV care access, such as distance to clinic. To date, community-based ART programmes have been mainly offered after ART initiation as a key to sustain ART adherence and retention in care [38, 39]. They could also be considered for ART initiation, at home for example [40], although the impact of such an intervention on long-term HIV follow-up is not yet known. The use of SMS reminders and the development of a tracking system including phone calls and home visits by community caregivers, as experienced in the TasP trial, have also been evaluated as effective to link [41] and retain people in care [42]. Secondly, as part of the differentiated ART delivery approach recommended by the WHO [43] aiming at simplifying HIV services and addressing the diversity of needs of people in care and treatment [44, 45], the delivery of 3-month ART supplies for all stable individuals should be facilitated in all clinics. Thirdly, HCPs also reported on the importance of reducing stigma in health care system, through the integration of HIV services within general primary care services, and especially with other long-term conditions, as reported in another study conducted in another rural setting in South Africa [46]. In this context, the South African government recently initiated the "Ideal clinic" programme [29], with the integration of HIV services as part of a comprehensive health package. This programme has not yet been evaluated but certainly provides more and new care opportunities for people living with HIV who do not see their infection as a priority. The wide scale implementation of integrated models of care would nevertheless need investments in training and capacity building support regarding multiple diseases and co-morbidities.

We acknowledge some limitations regarding this study. First, TasP HCPs reported their experiences of delivering universal ART in specific trial clinics, thus not quite in real life conditions. In addition, DoH HCPs were interviewed on their perceptions regarding universal ART, while they had not provided it at the time of the interviews. However, the declarations of both TasP and DoH HCPs regarding the provision of ART early in the course of the infection, and the perceptions of the universal ART scale-up were concordant. Secondly, among participants, only two males (one in the TasP counsellors FGD and one in the TasP nurses FGD) shared their experiences; the sample is however representative of the current gender distribution in the South African health facilities [47]. Third, the FGDs and IDIs were conducted in isiZulu then translated in English, a process that could have led to some loss of information; all the translations were however double-checked by the qualitative interviewer supervisor. Finally, this analysis is specific to a rural South African setting; further research in other settings, elsewhere in Africa or maybe in less HIV prevalent areas, would contribute to fully apprehend the

challenges of providing universal ART. The main methodological strength of this study is that there was a strong collaboration for creating the codebook between the qualitative interviewers (who collected, transcribed and translated the data from English to isiZulu) and the two main scientists (who analyzed the data).

In conclusion, while HCPs reported globally good experiences of offering ART at high CD4 counts, this study reflected specific challenges regarding its acceptation by the patients who do not feel sick and not see the value of initiating ART early or might need more time to accept and disclose their HIV status and to be ready to initiate ART for life. In this context, it is essential for HCPs to have appropriate skills and enough time with their patients to counsel them regarding early ART initiation. Insufficient and delayed linkage to care and treatment is problematic in the era of prompt and universal ART; further, if people are not on ART and are not virally suppressed, their risk of HIV transmission is high, thus contributing to sustained HIV incidence and fuelling the epidemic at population level, as demonstrated in the ANRS 12249 TasP trial [31]. Our results confirm that universal ART is more than an increase in ART threshold eligibility and raises challenges for patients, HCPs and decision-makers. It is crucial to continue developing, evaluating, and implementing innovative models of care in order to increase early linkage to and retention in HIV care and treatment and achieve the UNAIDS 90-90-90 target for UTT [48].

Supporting information

S1 Table. Analysis matric on experiences and perceptions of health care professionals regarding universal ART. Hlabisa sub-district, South Africa, 2016.
(DOCX)

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3.3. Care trajectories of people living with HIV in a UTT strategy

The results of the study entitled “From home-based HIV testing to viral suppression: HIV care trajectories in the context of Universal Test-and-Treat in rural South Africa.” are currently being reviewed by co-authors and the corresponding manuscript is being considered for submission to AIDS.

3.3.1. Background

UTT implies more than just increasing stocks of HIV testing kits and ART drugs in government clinics. It implies that, there is a system in place that empowers all inhabitants of a given community to check their HIV status regularly and start ART after a positive HIV diagnosis. The pathway from HIV diagnosis to continuing recovered health, often referred to as the HIV care cascade, has been shown to contain many important points of failure, including suboptimal linkage to and retention in HIV care, insufficient use of ART and suboptimal adherence to therapy [157]. As a consequence, decision makers have called for a better understanding of the facilitators and barriers at each step of the care cascade [163]. Increasingly, researchers are pointing out that health interventions that focus on specific cascade steps are unlikely to succeed in fixing the leaky cascade if they are not integrated in a more holistic approach that takes into account the whole continuum of care. It is unknown how individuals exposed to UTT react to the integration of innovative HIV interventions in their care routine. Evidence of patient care-seeking behaviours after HIV diagnosis should be key to design interventions that better fit people's care needs and support them throughout the care cascade.

3.3.2. Objective

We aimed to describe the timing and sequencing of individual HIV care statuses from referral to viral suppression, by identifying groups of individuals with similar trajectories and identifying factors associated with each group.

3.3.3. Methods

We used state sequence data analysis to identify homogeneous groups of care trajectories of TasP participants. Individual and cluster characteristics at referral were analysed using multinomial logistic regression to characterize the profile of each group (Table 2).

Table 2: Methodological details of the analysis of care trajectories of participants to the ANRS 12249 TasP trial

Work steps	Description
1. Data collection	• Data sources: three longitudinal databases: the TasP trial database, the AHRI clinical database (ACCDB), the National health laboratory services database (NHLS) • Data collected: epidemiological and health system information (e.g. local ART coverage, distance to the nearest clinic), demographic and socio-economic information, and clinical information (e.g. CD4 counts)
2. Creation of individual care trajectories	Construction of a unique care trajectory for each study participant starting from the day s/he was first ascertained HIV+ and referred to a trial clinic in the TasP trial, until the trial end Allocation of a care status at each day D of the period to each individual, among the four following: "not in care on day D", "in care, not on ART on day D", "in care on ART not virally suppressed on day D", "in care, on ART, virally suppressed on day D"
3.Population selected for the analysis	The study population was selected with the following criteria: • TasP participants (aged 16+ and resident) • ever ascertained HIV+ over the course of the trial through rapid HIV test or self-report • who were not already in HIV care in local government clinic at time of referral (referral being defined as the first time they were ascertained HIV+ within the TasP trial) • observed at least 18 months after referral
4. Statistical analysis	• Computation of similarities between individual care trajectories • Determination of homogeneous care trajectories groups: chosen partition based on hierarchical classification and with the highest relative loss of inertia • Description of care trajectories groups: description of the timing and sequencing of major care statuses (e.g. median time to enter into care since referral, ART initiation rate). • Analysis of factors associated with care trajectories groups using a multinomial logistic regression model

3.3.4. Principal results and discussion

After an HIV positive diagnosis, each person starts an individualized care trajectory that is its own. In the framework of the TasP trial, we were able to report on the high heterogeneity of individual care utilization patterns and speed from care referral to viral suppression. Our study confirmed the main features of the leaky care cascade, with linkage to care representing the major attrition point in the area. Beside the high proportion of people who remain outside of care after a positive HIV diagnosis, we were able to identify a large number of individuals who visited a clinic once after diagnosis and left thereafter, individuals who only visited a clinic six months after diagnosis and individuals who took over six months before initiating ART. Such results highlight the many missed opportunities of the health system to offer adequate care to individuals. Our results demonstrated the potential of repeated contacts with the healthcare system to retrieve people lost from care, underlying how efforts should be made to leverage any encounter with the health system to encourage people to embrace care in the long run [189]. This work showcased the existing gap between the healthcare offer and individuals healthcare expectations and needs. By embracing a person-centred approach, our work identifies that, maximizing the preventive benefits of ART on HIV transmission in a UTT strategy will require the scale up of differentiated care and support, especially between diagnosis and ART initiation in this rural South African study area.

3.3.5. Role of the PhD candidate

Supervised by two researchers, Joseph Larmarange and my PhD director Joanna Orne-Gliemann, I formulated the research question and identified the suitable statistical method to answer this project. Joseph Larmarange computed the daily care statuses from which I was able to create individual care trajectories and perform the statistical analysis using R software version 3.0.1. I wrote the first draft of the manuscript

TITLE

From home-based HIV testing to viral suppression: HIV care trajectories and the effect of immediate ART in the context of Universal Test-and-Treat in rural South Africa.

AUTHORS

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ABSTRACT

Background: The universal test-and-treat strategy requires that HIV-infected individuals enter care and start an antiretroviral treatment (ART) as soon as possible after diagnosis. Little is known yet about the care continuum in such context. We aimed to describe the timing and sequencing of individual HIV care status from referral to viral suppression by identifying groups of individuals with similar care trajectories and identifying factors associated with each group.

Methods: We used prospective longitudinal data from the ANRS 12249 TasP trial, a cluster-randomized trial that investigated the impact of immediate ART following home-based testing, on HIV incidence in rural KwaZulu-Natal, South Africa (2012-2016). The care status of all participants ≥16 years, identified HIV+, not in care at referral and followed-up for ≥18 months was classified at each calendar day: not in care, in care but not on ART, on ART but not virally suppressed, virally suppressed. We used state sequence data analysis to identify homogeneous care trajectories groups. A multinomial logistic regression was used to identify the profile of each group in terms of individual and cluster characteristics.

Results: 1,837 HIV+ participants were included. Median age was 34 years [IQR 27-45], 74% were female. We identified four care trajectories groups: (i) participants who mostly did not enter care (53%), (ii) participants with inconstant care, visiting a clinic occasionally but leaving care thereafter (median time to exit care: 11 months [5.3-13]) (14%), (iii) participants who took extensive time at each step of the care continuum (median time between care referral and ART initiation: 8.0 months [6.4-9.7]) (12%) and (iv) participants who rapidly progressed towards continuous care (median time between care referral and ART initiation: 1.2 month [0.6-2.7]) (21%). Participants who were living further than a kilometre from a clinic, who were newly diagnosed at referral and who were living in a cluster were immediate ART was not offered, were more likely to present with incomplete, inconstant and slow care trajectories.

Conclusions: Care trajectories are heterogeneous. The delivery of immediate ART increases an individual's likelihood to follow a quicker and more complete care trajectory. To maximise the impact of universal test-and-treat strategies, differentiated care and support should be scaled-up, especially between diagnosis and ART initiation, which constitutes the main bottleneck of HIV programs in this South African rural study area.
Keywords: Care trajectories, timing, state sequence data analysis, longitudinal data, immediate ART, HIV, South Africa

INTRODUCTION

At the end of the 2000 decade, the "Universal Test and Treat" (UTT) strategy emerged from mathematical modelling, with the promise of drastically reducing HIV incidence, especially in highly prevalent areas [1], based on the idea that "undetectable equals untransmittable" [2]. It implied offering regular HIV testing and counselling to an entire population, and ART to all those living with HIV, regardless of their immunological staging. In this context, the Joint United Nations programme on HIV/AIDS (UNAIDS) defined in 2014 the 90-90-90 targets for HIV treatment scale-up by 2020 (namely, that 90% of HIV-infected persons know their status; that 90% of those initiate and remain on ART; and that 90% of those have undetectable viral load). While UTT interventions have been designed to both lessen the burden of HIV infection and reduce vulnerability to HIV acquisition, little is known about their acceptability, feasibility and effectiveness on HIV incidence. Several research projects, including randomized controlled trials in Southern and Eastern Africa have been or are currently evaluating the field efficacy of UTT [3-7].

Immediate treatment implies more than just an increase of ART provision. It requires that, after a positive HIV diagnosis, people enter care, initiate ART and remain on treatment life-long. This pathway from HIV diagnosis to continuing viral suppression, often referred to as the HIV care cascade, has been shown to contain many important points of failure, including suboptimal linkage to and retention in HIV care, insufficient use of ART and suboptimal adherence to therapy [8]. At population level, failure along the cascade have resulted in excess loss of life [9, 10], missed opportunities for preventing sexual transmission of HIV [11], and accrued economic and social costs (e.g. productivity losses, increased healthcare costs, households impoverishment) [12, 13].

The ANRS 12249 TasP (TasP) trial is the first trial to yield results on immediate ART at population level: estimated HIV incidence was 2.11 per 100 person-years (95% confidence interval (CI) 1.84–2.39) in the intervention group and 2.27 per 100 person-years (2.00–2.54) in the control group (adjusted hazard ratio 1.01, 95% CI 0·87–1·17; p=0·89) [14]. It investigated the impact of immediate ART following home-based testing on HIV incidence in South Africa. It was highly successful in terms of HIV testing uptake (92%), and ART retention (85%), but suffered very low linkage to care rates: among people identified as HIV-positive in the trial and referred to care, only 47% had visited a clinic by 6 months [14]. If previous systematic reviews have efficiently examined facilitators and barriers of linkage to care [15-17], few have

holistically examined facilitators and barriers that are relevant across multiple steps within the HIV continuum of care [18]. Yet, such approach could contribute to integrate strategies at each of these points into sustainable systems for improving HIV service delivery [19]. As a consequence, innovative research that goes beyond the traditional care cascade research could contribute to better understanding patient care-seeking behaviours after HIV diagnosis and improve the current models of care to pay attention to the full continuum of care [20].

In the last decade, there has been an increasing interest in individual life course approaches applied to the study of individual healthcare patterns over time [21]. They define an individual care trajectory as a succession of time-dependent care statuses, taking into account that trajectories vary according to multiple factors of the context in which they happen (geographical, political, economic, behavioural, social) [22, 23]. In the HIV field, not only this person-specific approach allows taking into account the reality of patients cycling in and out of care (unlike traditional care cascade approaches which depict a linear engagement in care [24]), but it is matched to the imperative to understand the individual case and to tailor HIV care interventions to optimize individual health outcomes [21-23, 25].

We aimed to describe the timing and sequencing of individual HIV care statuses from clinic referral to viral suppression in rural South Africa, by identifying groups of individuals with similar trajectories and identifying factors associated with each care trajectories group. Ultimately, we aimed to inform the design and management of healthcare services to optimize the health benefits of ART.

METHODS

Study setting and design

The ANRS 12249 TasP trial was a phased two-arm cluster-randomised trial implemented by the African Health Research Institute (AHRI) in Hlabisa sub-district, northeast KwaZulu-Natal, South Africa, in a rural area with approximately 28,000 isiZulu-speaking resident adults. Adult HIV prevalence in the sub-district was around 30% [26, 27]. The trial aimed to investigate whether immediate ART initiation offered to all HIV-positive individuals, identified through home-based HIV testing will reduce HIV incidence in the area. Trial protocol and study procedures have previously been reported in detail [5, 28]. The trial was implemented from 9 March 2012 to 30 June 2016 using a phased approach: 4 clusters were opened in 2012, 6 additional clusters opened in 2013 and 12 in 2014, all 22 clusters (2×11) were followed until mid-2016.

The UTT strategy tested in the TasP trial had two main components: (i) repeated home-based HIV testing in both study arms and (ii) immediate ART initiation (intervention arm) vs. national ART initiation guidelines (control arm). In both trial arms, HIV counsellors visited all local households and enumerated all resident adult (16 years and above) household members (initial census of the population during the first survey round). At each six-monthly subsequent home-based survey round, newly identified households and all previously registered households were (re)visited and the list of resident adult household members was updated. Eligible individuals providing written informed consent in isiZulu responded to a socio-demographic questionnaire and gave a finger prick sample collected as a dried blood spot (DBS), used for HIV incidence estimation. HIV counsellors offered individuals point-of-care rapid HIV counselling and testing. All trial participants identified as HIV-positive (through rapid test or self-report) were referred to a local trial clinic situated in the trial cluster in which they lived.

In the control clusters, HIV-positive adults were offered ART according to national guidelines (initially CD4 count ≤350/μL, then ≤500/μL from January 2015). In the intervention clusters, all HIV-positive adults seen in trial clinics were offered the opportunity to begin ART immediately regardless of CD4 count or clinical staging. The trial area was also served by three local governmental clinics of the department of health providing HIV testing, HIV care and ART according to national guidelines [29]. HIV-positive participants could opt to receive HIV care in local governmental clinics or transfer to a trial clinic.

The Biomedical Research Ethics Committee (BREC), University of KwaZulu-Natal, South Africa (BFC 104/11) and the Medicines Control Council of South Africa approved the trial. The trial was also registered on ClinicalTrials.gov: NCT01509508 and South African National Clinical Trials Register: DOH-27-0512-3974.

Sources of data

Information on residency and trial exits (updated every survey round at household level); socio-demographic and economic characteristics (collected at every clinic registration through individual questionnaires); uptake and results of home-based HIV testing (rapid tests offered every round); third generation ELISA HIV serological results from DBS (collected every

round); and clinic visits, ART prescriptions and viral loads of HIV-positive participants seen in trial clinics, were available from the trial database for these analyses.
Two additional data sources were used to capture information from people living with HIV seen in local governmental clinics: (a) viral loads and CD4 counts from National Health Laboratory Service (NHLS); and (b) ART clinic visits and ART prescriptions from the AHRI clinical database (ACCDB) which is managed by the Hlabisa Department of Health and AHRI. Both NHLS and the ACCDB databases contain data from Hlabisa primary care clinics since 2004 [29]. Linkage between trial, NHLS and ACCDB databases used a probabilistic score based on first name, last name, date of birth, South African ID number and cell phone number. Matching of the databases was approved by the BREC in March 2013 (protocol amendment 4).

Daily statuses

We built a unique care trajectory as a succession of daily statuses for each study participant, starting from the day s/he was first ascertained HIV+ and referred to a trial clinic, until the trial closure. We considered four daily statuses: (i) diagnosed but not actively in care; (ii) actively in care but not on ART; (iii) on ART but not virally suppressed (undocumented viral load or viral load over 400 copies/μL); and (iv) in care, on ART and documented viral suppression. Those daily statuses were defined using the following variables:
Being actively in HIV care in a trial clinic was defined as not being >90 days late of a scheduled clinic appointment date. Although there is no consensus in literature on how to measure retention in care, more than 3 months since last scheduled visit was used in several studies as a measure of loss to follow-up [30]. For individuals receiving HIV care in local governmental clinics, we used two different definitions, due to the nature of the data available in NHLS and ACCDB databases which are not exhaustive (some individuals recorded in one database were not found in the other). Therefore, being actively in HIV care in a local governmental clinic was defined as having a clinic visit recorded in the last 4 months in ACCDB database (this database is limited to patients on ART who are supposed to visit clinics monthly) or as having a CD4 count or a viral load recorded in the NHLS database in the previous 13 months [31], CD4 count and viral load data being considered as a proxy for clinic visits.
Being on ART was defined as having an ART prescription recorded in the trial or the ACCDB database in the previous 3 months or as having an undetectable viral load (< 400 copies/μL) recorded in the last 13 months in the NHLS database, an undetectable viral load being considered here as a proxy for being on ART.
Viral suppression was defined as having a viral load less than 400 copies/μL. The viral load at a given date was estimated by linear interpolation using all results recorded in the trial and the NHLS databases. Viral load was considered as undocumented before the first available record.

Individual and cluster-level characteristics

Individual and cluster-level characteristics were computed at referral using the closest available individual questionnaire. Missing sociodemographic characteristics were imputed using a regularised iterative FAMD (factorial analysis for mixed data) algorithm [32] implemented in missMDA R package. Local HIV prevalence and local ART coverage were computed using a Gaussian kernel density estimation with a fixed banwidth of three kilometres.

Population selected for the analysis

The study population was selected with the following criteria: (i) TasP participants (aged 16+ and resident), (ii) ever ascertained HIV+ by a fieldworker during/over the course of the trial through rapid HIV test or self-report and therefore referred to HIV care; (iii) who were not already in HIV care in local governmental clinic at time of referral (referral being defined as the first time they were ascertained HIV+ within TasP); (iv) observed at least 18 months after referral (i.e. they didn't exit the trial population in the following 18 months (out-migration, death) or they were referred to HIV care at least 18 months before trial closure).
The criteria (iv) was included to the definition of the study population to reach a compromise between a reasonable number of individuals – thus being representative of the situation, and long enough follow-ups – thus depicting meaningful trajectories. Indeed, follow-up periods strongly differed between individuals mainly due to the trial design. Depending on where participants lived, they were enrolled in the trial between either 2012, 2013 or 2014 to be follow-up until the trial end in 2016. Among the 4,203 participants who met the criteria (i), (ii) and (iii), 353 were followed-up for at least 36 months, 762 for at least 24 months, 1,816 for at least 18 months, 2,711 for at least 12 months and 3,496 for at least 6 months.

Statistical analysis
The statistical analysis was led in three phases:

1. Identification of care trajectories groups
The care trajectory of an individual is defined as her/his 548 successive daily care statuses following referral. To compare dissimilarity between care trajectories, optimal matching was used to compute a distance matrix between individuals using TraMineR R package (REF: https://www.jstatsoft.org/article/view/v040i04) and a hierarchical matrix of costs (e.g. considering that transitioning from "not in care" to "on ART but not virally suppressed" has a cost of 2 while transitioning from "not in care" to "in care but not on ART" has a cost of 1). From that distance matrix , a dendrogram (hierarchical clustering) was computed using the Wald algorithm (REF: http://www.jstor.org/stable/2282967), from which we divided them into homogeneous care trajectories groups. The chosen partition was based on the highest relative loss of inertia criterion (adapted from HCPC function in FactoMineR package) [33]

2. Description of care trajectories groups
We described the different groups of care trajectories by depicting the timing and sequencing of major care events: entry into care, ART initiation, viral suppression and exit of care. Descriptive indicators used included the number of individuals experiencing the care event, the rate of care event and the median time to care event. Other variables were also used to describe the care trajectories groups such as the trial arm to which participants were assigned (control vs intervention arm), the health care system that they used for their first clinic visit (trial vs governmental clinic) and their CD4 count at first clinic visit.

3. Analysis of factors associated with care trajectories groups
We performed univariate analyses (Chi^2 test) between care trajectories groups and variables depicting individual and cluster-level data at care referral: socio-demographic and economic characteristics (sex, age, education, professional status, household wealth assets), local health

system characteristics (local HIV prevalence at clinic referral, local ART coverage at clinic referral, straight line distances between one's homestead and the nearest trial clinic, the nearest governmental clinic or the national road), individual perception of immediate ART (think that ART makes people with HIV less infectious, is less worried now that treatments have improved, would accept to start ART as soon as s/he learns about his/her positive status), trial-specific characteristics (trial arm) and previous HIV care experience (never in care and newly diagnosed, never in care and already diagnosed, previously in care but lost to follow-up). Variables with a p-value lower than 25% in univariate analyses were included in a multinomial logistic regression model. A manually step-down procedure was used to select the best model for each cluster using the Akaike Information Criteria (AIC). All analyses were performed using R 3.0.1.

RESULTS

The study population included 1,837 individuals (Figure 1).

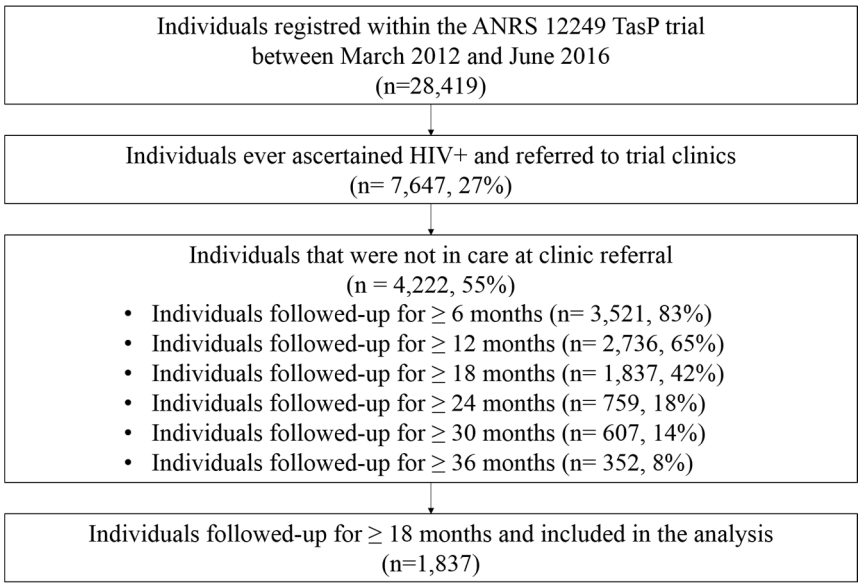


Figure 1: Flow chart of inclusion of the study population (ANRS 12249 TasP trial, rural South Africa)

Analysis of care trajectories

The quantitative comparison of similarities between care trajectories allowed us to organize them into a dendrogram (Supplementary file 1). Based on the highest relative loss of inertia criterion, we identified four homogeneous care trajectories groups, which are presented in Figure 2.

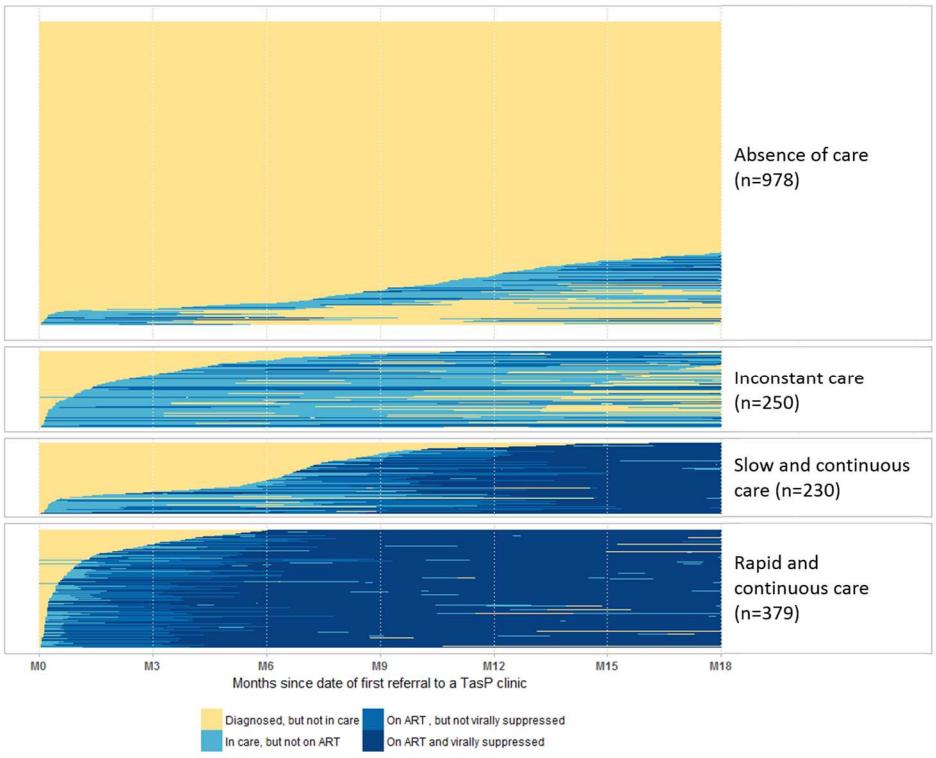


Figure 2: Individual care trajectories by care trajectories group, participants to the ANRS 12249 TasP trial who were not already in care when referred to a trial clinic (n=1,837).

ART: antiretroviral treatment. Each horizontal line (Y-axis) represents a unique individual and the height of the group represents its proportion of the studied population. The X-axis represents time since referral to HIV care. The colours represent the daily care statuses.

Description of care trajectories groups

Group 1 (labeled “absence of care” by the authors for convenience, n=978, 53.2% of study population) gathered participants who mostly never entered care (n=742, 76%, see Table 1).

In group 2 (“inconstant care”, n=250, 13.6%), all participants entered care and almost half of them had a CD4 count above 500 cells/mm^3 (n=116, 46%). Half of the participants had initiated ART (n=119, 50%), and did so in the four months following care referral (median 4.7 [1.4-11]). A large majority of participants exited care during the follow-up period (n=154; 62%), mostly prior ART initiation (n=148, 96%).

In group 3 (“slow and continuous care”, n=230, 12.5%), all participants entered care in a median of six months following care referral (6.1 [1.1-7.7]). They all initiated ART in the eight months following care referral (median 8.0 [6.4-9.7]) and attained virally suppression after a median of 2.8 months [0-3.7].

In group 4 (“rapid and continuous care”, n=379, 20.6%), all participants entered care in a median of 15 days following care referral (0.4 months [0.2-1.2]). Almost half of them had a CD4 count $\leq$ 350 cells/mm^3 (n=164, 43%). They all initiated ART in the month following care referral (median 1.2 [0.6-2.7] and attained virally suppression after a median of 2.7 months [0-3.1].

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Table 1: Description of the four care trajectories groups. ANRS 12249 TasP trial, rural south Africa, 2012-2016 (n=1,837).

Descriptive indicators	Care clusters				
	Absence of care	Inconstant care	Slow and continuous care	Rapid and continuous care	All
All individuals (a)	978	250	230	379	1,837
Intervention arm	461 (47%)	75 (30%)	110 (48%)	214 (56%)	860 (47%)
Entry into care					
Entered care (at least one clinic visit) (b)	236	250	230	379	1095
Entry into care rate (b/a)	24%	100%	100%	100%	60%
Median time to enter care since referral (months) (among b)	9.2 [3.8-12.8]	1.3 [0.3-3.7]	6.1 [1.1-7.7]	0.4 [0.2-1.2]	1.5 [0.2-6.7]
CD4 count at first clinic visit* (among b)					
median	466[271-625]	498 [315-651]	415 [256-564]	371 [244-568]	428 [266-610]
ART initiation					
Have initiated ART (d)	108	119	230	379	836
ART initiation rate (d/b) (%)	46%	48%	100%	100%	76%
Median time between care referral and ART initiation (among d) (months)	12 [8.0-15]	4.7 [1.4-11]	8.0 [6.4-9.7]	1.2 [0.6-2.7]	3.7 [0.99-8.7]
Viral suppression					
Have attained viral suppression (e)	52	43	230	379	704
Viral suppression rate (e/d) (%)	48%	36%	100%	100%	84%
Median time between ART initiation and viral suppression (among e) (months)	2.8 [0.96-3.4]	4.3 [2.4-11]	2.8 [0-3.7]	2.7 [0-3.1]	2.8 [0-3.6]
Exit from care					
Exited care (f)	109	154	32	40	335
Care exit rate (f/b)	46%	62%	14%	10%	30%
Median time to exit care (among f) (months)	4.0 [3.4-4.7]	11 [5.3-13]	4.0 [3.9-5.7]	13 [9.2-13]	6.0 [4.0-13]

ART: antiretroviral treatment, IQR: interquartile range, *first CD4 count in the three months following the first clinic visit.

Analysis of factors associated with care trajectories groups

Table 2 presents the characteristics of the study participants at the time of their first referral to a TasP clinic. The median age was 34 (interquartile range [IQR]: 27-45) and there was a majority of women (74%). Most participants had poor socio-economic status: only 23% completed secondary school and 77% reported being inactive (neither employed nor student). Local adult HIV prevalence ranged from 13% to 60% (median = 35% [29-39] and local ART coverage ranged from 15% to 63% (median =38% [33-43]). The median distance to the national road was 2.4 km [1.1-5.5]. Most participants were less than two km away from a trial clinic (n=1,541, 83%), and further than three km from a governmental clinic (n=1,491, 81%). A large majority of participants had positive views towards ART: 84% thought that ART makes people less infectious, 89% were less worried now that ART have improved, 94% would accept to start ART as soon as they learn about their HIV-positive status.

Participants from the care trajectories group "absence of care" were more likely to be newly diagnosed than those of the "rapid and continuous care" group (never in care and already diagnosed: adjusted odd ratio [aOR] = 0.25, 95% confidence interval [CI] = 0.14-0.43; previously in care but lost to follow up: aOR=0.14, CI = 0.08-0.25) (Table 3 and 4). They were also more likely to have been allocated to the control arm of the trial (aOR = 0.61, CI = 0.47-0.82).

Similar results were found for participants to the "inconstant care" group (never in care and already diagnosed: aOR = 0.31, CI = 0.16-0.60; previously in care but lost to follow up: aOR = 0.36, CI = 0.18-0.71).

On the contrary, participants from the care trajectories group "slow and continuous care" didn't present significant differences in terms of HIV care history when compared to those of the "rapid and continuous care" cluster. They were not significantly more likely to have been allocated to the control arm of the trial. Moreover, they were more likely to live in an area where the HIV prevalence was less than the median (35.3%) (aOR: 0.63, CI = 0.43-0.88).

Table 2: Characteristics of the four care trajectories groups, ANRS 12249 TasP trial, rural South Africa, 2012-2016 (N=1,837)

	Study population		Absence of care	Inconstant care	Slow and continuous care	Rapid and continuous care	p-value (chi² test)
	n	%					
HIV care history							
HIV care status at clinic referral							
Never in care, newly diagnosed in TasP	244	13%	**188 (19%)**	32 (13%)	**8 (3%)**	**16 (4%)**	
Never in care, already diagnosed	1042	57%	574 (59%)	124 (50%)	124 (54%)	220 (58%)	< 0.01
Previously in care but lost to follow up	551	30%	**216 (22%)**	**94 (37%)**	**98 (43%)**	**143 (38%)**	
Socio-demographic and economic characteristics							
Gender							
Male	469	26%	256 (26%)	60 (24%)	60 (26%)	93 (25%)	0.86
Female	1368	74%	722 (74%)	190 (76%)	170 (74%)	296 (75%)	
Age (years)							
16-19	95	5%	37 (6%)	15 (6%)	10 (4%)	13 (3%)	
20-29	560	30%	**3393 (35%)**	86 (34%)	62 (27%)	**73 (19%)**	
30-39	522	28%	265 (27%)	74 (30%)	**83 (36%)**	100 (26%)	< 0.01
40-49	339	19%	174 (18%)	42 (17%)	41(18%)	82 (22%)	
Over 50	321	18%	**143 (15%)**	33 (13%)	34 (15%)	**111 (29%)**	
Education level							
Primary school or less	756	41%	371 (38%)	97 (39%)	90 (39%)	**198 (52%)**	
Some secondary school	655	36%	359 (37%)	94 (39%)	89 (39%)	123 (32%)	< 0.01
At least completed secondary school	416	23%	248 (25%)	59 (22%)	51 (22%)	**58 (15%)**	
Professional status							
Employed	279	15%	152 (16%)	31 (12%)	31 (13%)	65 (17%)	
Student	142	8%	**98 (8%)**	19 (8%)	11 (5%)	**14 (4%)**	< 0.01
Looking for work	528	29%	298 (30%)	73 (29%)	75 (33%)	**84 (22%)**	
Other inactive	888	48%	432 (44%)	127 (51%)	112 (49%)	**216 (57%)**	
Household wealth assets*							
Low	701	38%	360 (37%)	101 (40%)	86 (38%)	154 (41%)	
Middle	719	39%	376 (38%)	104 (34%)	104 (45%)	155 (41%)	0.01
High	415	23%	241 (25%)	39 (26%)	39 (17%)	70 (18%)	
Missing	2	0%	1 (0%)	0(0%)	1(0%)	0(0%)	
Health system							
Local HIV prevalence (%)							
< 35.3	918	50%	502 (51%)	111 (44%)	125 (54%)	180 (47%)	0.08
≥ 35.3	919	50%	476 (49%)	139 (56%)	105 (46%)	199 (53%)	
Distance from home to the nearest HIV-dedicated trial clinic (km)							
< 1	669	36%	324 (33%)	103 (41%)	91 (40%)	151 (40%)	
[1-2[	872	48%	472 (48%)	122 (49%)	112 (49%)	166 (44%)	<0.01
≥ 2	296	16%	182 (19%)	**25 (10%)**	27 (12%)	62 (16%)	
Distance from home to the nearest primary health care governmental clinic (km)							
<3	346	19%	**216 (22%)**	35 (14%)	36 (16%)	59 (16%)	
[3,5[	492	27%	260 (27%)	79 (32%)	68 (30%)	85(22%)	< 0.01
[5,7[	665	36%	325 (33%)	87 (35%)	92 (40%)	**161(42%)**	
≥ 7	334	18%	177 (18%)	49 (20%)	34 (15%)	74 (20%)	
Distance to N2							
<1	394	21%	214 (22%)	67 (27%)	44 (19%)	69 (18%)	
[1,3[	649	36%	323 (33%)	90 (36%)	82 (36%)	154 (41%)	0.03
[3,5[	282	15%	167 (17%)	29 (12%)	30 (13%)	56 (15%)	
≥ 5	512	28%	274 (28%)	64 (26%)	74 (32%)	100 (26%)	
Perception of HIV stigma							
Agree that people avoid people living with HIV							
Agree	556	30%	311 (32%)	74 (30%)	66 (29%)	105 (28%)	0.45
Disagree/Do not know /missing	1281	70%	667 (68%)	176 (70%)	164 (71%)	274 (72%)	
Agree that people do not blame people living with HI							

Agree	1065	58%	562 (57%)	138 (55%)	143 (62%)	222 (59%)	0.45
Disagree/Do not know /missing	772	42%	416 (43%)	112 (45%)	87 (38%)	157 (41%)	
Know a family member living with HIV							
Agree	617	34%	307 (31%)	98 (39%)	78 (34%)	134 (35%)	0.10
Disagree/Do not know /missing	1220	66%	671 (69%)	152 (61%)	152 (66%)	245 (65%)	
Perceptions of ART							
Think that ART makes people with HIV less infectious.							
Agree	1540	84%	831 (85%)	196 (78%)	191 (83%)	322 (85%)	0.07
Disagree / Do not know / Missing	297	16%	147 (15%)	54 (22%)	39 (17%)	57 (15%)	
Is less worried now than treatment have improved							
Agree	1631	89%	879 (90%)	218 (87%)	204 (89%)	330 (87%)	0.40
Disagree / Do not know / Missing	206	11%	99 (10%)	32 (13%)	26 (11%)	49(13%)	
Would accept to start ART as soon as s/he learn about her/his HIV positive status							
Agree	1721	94%	911 (93%)	232 (93%)	216 (94%)	362 (96%)	0.39
Disagree / Do not know / Missing	116	6%	67 (7%)	18 (7%)	14 (6%)	17 (4%)	
Trial-specific							
Trial arm							
Control arm	977	53%	517 (53%)	**175 (71%)**	120 (52%)	**165 (44%)**	<0.01
Intervention arm	860	47%	461 (47%)	**75 (29%)**	110 (48%)	**214 (56%)**	

ART: antiretroviral treatment; * Household wealth assets had been defined in three categories (low, middle and high) in agreement with a principal component analysis considering sources of energy, amenities and access to drinking water and toilet facilities in this populations; Missing values were imputed for the following variables: Age group (n=96), Highest education obtained (n=1), professional status (n=3); Missing values for the following variables are: Household wealth assets (n=2), Agree that people avoid people living with HIV (n=10), Agree that people do not blame people living with HIV (n=10), Know a family member living with HIV (n=1), Agree that ART make people with HIV less infectious (n=7), Agree to start ART as soon as s/he learn about her/his HIV-positive status (n=11), Agree that is less worried now than treatment have improved (n=6),

Table 3: Adjusted multinomial logistic regression model with "Rapid and continuous care" as the reference category, ANRS 12249 TasP trial, rural South Africa, 2012-2016 (N=1,835)

	Absence of care Vs Rapid and continuous care (n= 994)		Inconstant care Vs Rapid and continuous care (n= 214)		Slow and continuous care Vs Rapid and continuous care (n= 228)	
	aOR [CI95%]	p-value	aOR [CI95%]	p-value	aOR [CI95%]	p-value
HIV care history						
HIV care status at clinic referral						
Never in care, newly diagnosed in TasP	1		1		1	
Never in care, already diagnosed	**0.25 [0.14-0.43]**	**<0.01**	**0.31 [0.16-0.60]**	**<0.01**	1.19 [0.49-2.88]	0.70
Previously in care but lost to follow up	**0.14 [0.08-0.25]**	**<0.01**	**0.36 [0.18-0.71]**	**<0.01**	1.40 [0.57-3.43]	0.47
Socio-demographic and economic characteristics						
Age (years)						
16-19	1		1		1	
20-29	1.37 [0.69-2.69]	0.37	1.10 [0.48-2.52]	0.82	1.04 [0.42-2.56]	0.86
30-39	0.85 [0.43-1.66]	0.63	0.70 [0.31-1.61]	0.40	0.99 [0.41-2.40]	0.97
40-49	0.67 [0.34-1.32]	0.77	0.45 [0.19-1.07]	0.07	0.57 [0.22-1.42]	0.22
Over 50	**0.40 [0.20-0.78]**	**<0.01**	**0.27 [0.11-0.64]**	**<0.01**	**0.35 [0.14-0.88]**	**0.02**
Household wealth assets*						
Low	1		1		1	
Middle	1.03 [0.77-1.37]	0.84	0.71 [0.48-1.04]	0.08	1.14 [0.78-1.66]	0.49
High	**1.42 [1.00-2.01]**	**0.05**	1.08 [0.69-1.69]	0.74	0.94 [0.58-1.53]	0.81
Health system						
Local HIV prevalence (%)						
< 35.3	1		1		1	
≥ 35.3	1.03 [0.77-1.34]	0.85	1.12 [0.77-1.64]	0.55	**0.63 [0.43-0.93]**	**0.02**
Distance from home to the nearest TasP clinic (km)						
< 1	1		1		1	
[1-2[	**1.32 [1.00-1.74]**	**0.05**	1.06 [0.74-1.51]	0.76	1.10 [0.77-1.60]	0.59
≥ 2	1.35 [0.90-2.01]	0.14	0.61 [0.34-1.10]	0.10	0.61 [0.34-1.07]	0.09
Distance from home to the nearest governmental clinic (km)						
<3	1		1		1	
[3,5[	**0.63 [0.42-0.95]**	**0.03**	1.04 [0.60-1.80]	0.89	1.36 [0.78-2.38]	0.28
[5,7[	**0.47 [0.32-0.69]**	**<0.01**	0.65 [0.38-1.12]	0.12	1.06 [0.62-1.81]	0.82
≥ 7	**0.53 [0.34-0.82]**	**< 0.01**	0.75 [0.41-1.38]	0.4	0.88 [0.47-1.64]	0.69
Trial-specific						
Trial arm						
Control arm	1		1		1	
Intervention arm	**0.61 [0.47-0.80]**	**<0.01**	**0.31 [0.22-0.44]**	**< 0.01**	0.72 [0.51-1.01]	0.06

aOR: adjusted odd ratio, 95CI: 95% confidence interval; ART: antiretroviral treatment.

DISCUSSION

Our results show the high heterogeneity of the care trajectories of participants to the TasP trial that were not in care at clinic referral. Four homogeneous care trajectories groups could be identified: (i) participants who mostly did not enter care (53%), (ii) participants with inconstant care, visiting a clinic occasionally but leaving care thereafter (14%), (iii) participants who took extensive time at each step of the care continuum (12%) and (iv) participants who rapidly progressed towards continuous care (21%). Unlike the care cascade model which describes at the population level how patients pass through statuses of HIV care (HIV testing, linkage to care, ART initiation and then viral suppression) [34], the care trajectories approach considers the multiple paths that individuals are susceptible to take through these statuses using individual-level data. These findings participate in understanding the mechanisms underlying the leaky care cascade.

Complex entry into care in the era of UTT

Our study shows that the vast majority of trial participants experienced difficulties with regards to linkage to care: no linkage to care (they remain outside of care after being ascertained HIV-positive (group 1), unsuccessful/incomplete linkage to care (visiting a clinic only once with no come back, group 2) or late linkage to care (≥6 months) (group 3)). Such results confirmed results of other studies that pointed out linkage to care as a major point of attrition of the care cascade in the trial area [14, 35], and more largely in this rural area of South Africa [31, 34].

Our study also brings evidence of people's acceptance of the offer of immediate ART, when national guidelines on CD4 thresholds have now been changed nationally, based on clinical practices and without any regard to the subsequent social consequences [36]. The study results support the reluctance of recent modelling studies regarding the potential of eliminating CD4 thresholds to achieve the full preventive benefits of ART/to maximize the preventive effects of ART on HIV transmission. Bor et al (2017) pointed out that even though the patients in a neighbouring area to the TasP trial area have blood drawn for a CD4 count once (and are therefore considered inappropriately as "linked to care"), many of them actually never return to the clinic to receive their CD4 results and initiate ART (and therefore contribute to HIV transmission) [37]. Those patients correspond to the group "inconstant care" of our study. Mc Creesh et al (2017) highlighted that, despite an increased number of people initiating ART with the elimination of the CD4 thresholds, many are likely to not reach viral suppression if they don't successfully retain in care (and therefore will continue to play a large role in HIV transmission) [38].

To achieve the full benefits of treatment as prevention, it is important to consider that entry into care is a complex process that encompasses the multiple care steps of an individual until s/he receives a chronic care enabling her/him to reach viral suppression [39]. Therefore, considering that someone is linked to care once he visited a clinic is not enough to fully measure engagement into care. This process is likely to include forward and backward steps, especially in the first months after clinic referral [24].

Potential of immediate ART to improve care trajectories

Our study shows that the most important factor that promises successful care trajectories is the suppression of the pre-ART period and the delivery of ART regardless of immunological or clinical staging (intervention arm). This result brings depth to the TasP transversal analyses that were not able to show a significant difference of linkage to care by trial arm [35].

This result suggests that structural characteristics of the health system such as the availability of health services are more likely to drive people towards successful care trajectories than individual profiles. This result supports the recent findings of mathematical modelling studies, which have shown that achieving the maximum population-level prevention benefits from the proposed UTT strategies is

dependent on successful programmatic outcomes, including optimum linkage to care rates and consideration of population mobility [40]. Changes in testing and ART initiation procedures, interventions to increase demand for immediate ART as well as improved retention on ART are needed [41].

Further, factors generally associated with poor linkage to and retention in HIV care such as low socio-economic characteristics, active employment, male gender, young age and fear of stigma [15, 16] were mostly not conclusively associated with care trajectories. The distance to the clinics, and the type of care offer (TasP clinic vs governmental clinic) didn't appear as factors that impact on care trajectories, therefore ruling out distance to the clinics as a barrier to access to care. And high household wealth assets were positively associated with the absence of care, possibly due to the fact that economically fortunate participants chose other care offers than those provided in the trial and the government, as it has been described in other studies in Sub-Saharan Africa [42].

Potential of universal repeat testing to improve care trajectories

This work shows that there is an heterogeneity of care trajectories in terms of speed and care utilization patterns, including individuals who never enter care or are lost from care. New diagnosis of HIV infection was strongly associated with suboptimal care trajectories (groups 1 and 2). This result confirms that, even in a context where repeat testing and support for linkage to care are provided, newly diagnosed individuals display poor care utilization behaviours, illustrating their high vulnerability [43, 44]. It also suggests that repeated contacts with the health care system, including repeated testing, have the potential to retrieve people who previously slipped through the cracks of the continuum of care [45, 46]. Failure of the health systems to retain individuals, despite several contacts with them, underline the gap between the healthcare offer and individuals' healthcare expectations and needs. These results emphasize that first medical appointments contacts can serve as catalysts/can be leveraged to encourage people to embrace care in the long run, therefore maximizing ART preventive potential. They add up to those of other studies in sub-Saharan Africa that pointed out how individuals who decline treatment or are lost to follow-up ultimately engage (or re-engage) in care. A successful first medical appointment may be a key factor influencing outcomes of strategies of early testing and treatment [40]. Person-centred approaches are required to empower healthcare professionals in delivering individualized quality services that will succeed in encouraging vulnerable subpopulations to go through all the steps of the care cascade in a timely manner [15, 47]. Besides, this work emphasizes the crucial role that an information system could play to efficiently record the HIV care history of individuals as well as contact tracing information, allowing care providers to follow-up on their patients care utilization, especially in areas where the population is highly mobile [48, 49].

Limitations

Our study has three main limitations: (i) we were not able to measure the care received outside of the Tasp trial and local governmental clinics (as private sectors, or people seeking care outside of the Hlabisa area, such as in Hluhluwe or Richards Bay); (ii) retention is not properly measured for individuals that were recorded in the NHLS database but not in the ACCDB database (window of 13 months). As a consequence, we were only able to measure people visiting Tasp clinics only once, but couldn't measure correctly individuals visiting governmental clinics only once, therefore underestimating the care trajectories group "inconstant care". To prevent any excessive interpretation, we provided all assumptions in the Methods section of the manuscript. Moreover variables that have been shown to impact specific steps of the care continuum and could therefore impact on the care trajectories couldn't be included in the multinomial analysis because they weren't available. For example, the CD4 count at clinic referral couldn't be included in the analysis. Yet, Boyer at al., showed that TasP participants with a CD4 count < 350 initiated ART earlier than those with a higher CD4 count

[50]. Then, the follow-up period was set up to 18 months, therefore occulting the reality of long term engagement in care, including crucial events that impact individual care such as migration and care exit. To oppose that impairment, we conducted sensibility analyses with individuals that were followed-up for 30 months. There were no significant difference in the main findings. Finally, as we intended to analyse the links between trajectories and covariates, we gathered trajectories in clusters. Even though those clusters were assessed homogeneous statistically, such analysis eclipses the inherent inter-individual variability of the trajectories [51].

Conclusion

The diachronic and longitudinal approach of our work highlighted the heterogeneity of individual care utilization behaviours, as well as identified typical patterns in the trajectories. By embracing a person-centred approach, it complements the traditional population-based approaches and brings a new perspective on the features of the leaky HIV care cascade. The present study highlights that, to maximise the impact of UTT strategies, differentiated care and support should be scaled-up, especially between diagnosis and ART initiation, which constitutes the main bottleneck of HIV programs in this South African rural study area.

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AUTHOR CONTRIBUTION

DP, JL, JOG developed the study concept, led interpretation of analysis, and drafted the article. JL contributed to the dataset collection and study implementation. JL and MHD computed daily care statuses. DP performed the statistical analysis. JL and MHD provided technical support. JOG and JL contributed key input and direction to all phases of the project, from study design to article writing.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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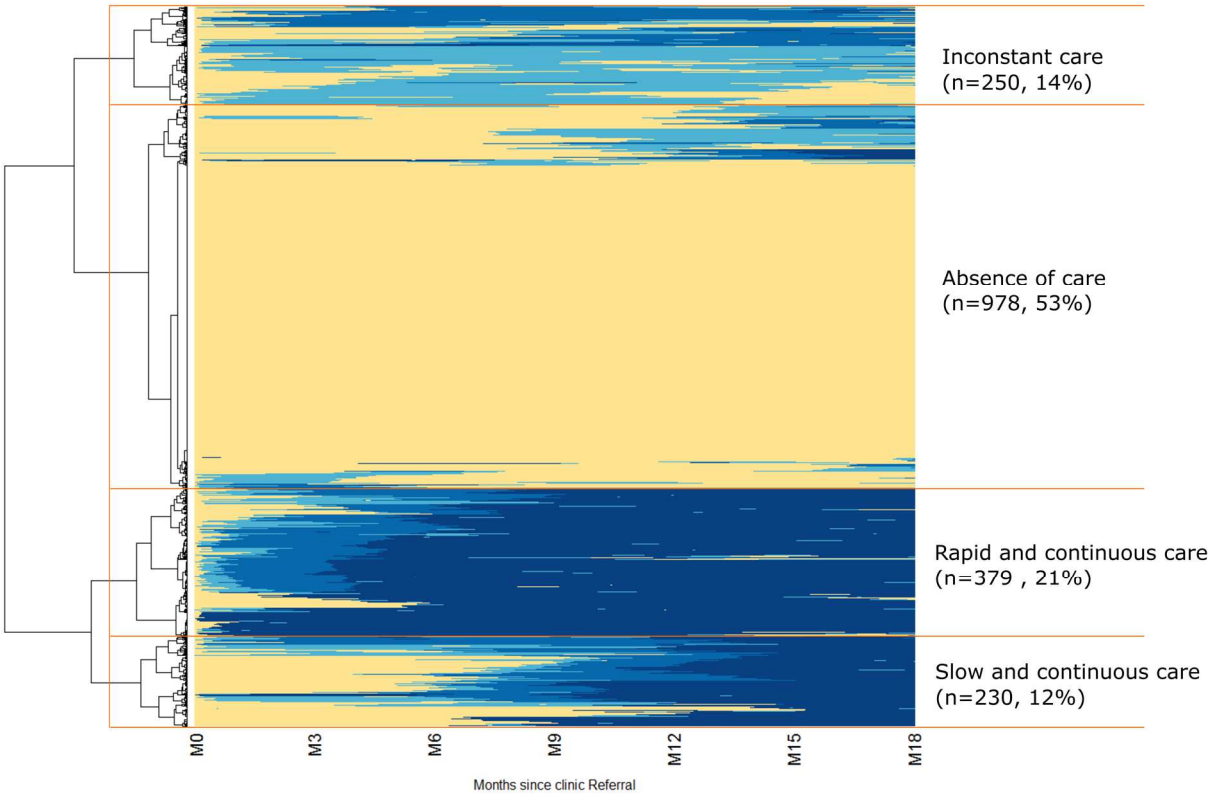
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Supplementary file 1: HIV care trajectories of the study participants, ordered in a dendrogram according to the Wald algorithm, ANRS 12249 TasP trial, rural South Africa, 2012-2016 (n=1,837)



Supplementary file 2: Additional descriptive indicators of the care trajectories groups. ANRS 12249 TasP trial, rural South Africa, 2012-2016 (n=1,837)

Descriptive indicators	Care clusters				
	Absence of care	Inconstant care	Slow and continuous care	Rapid and continuous care	All
Entry into care					
CD4 count at first clinic visit* (among b)					
≤ 350 cells/mm^3	70 (30%)	68 (27%)	75 (33%)	164 (43%)	377 (34%)
> 350 and ≤ 500 cells/mm^3	48 (20%)	50 (20%)	67 (29%)	74 (19%)	239 (22%)
> 500 cells/mm^3	96 (41%)	116 (46%)	67 (29%)	124 (33%)	403 (37%)
Missing	22 (9%)	16 (6%)	21 (9%)	17 (4%)	76 (7%)
Entry into TasP care					
First clinic visit in TasP (vs government) (c)	163	142	173	337	815
Entry into TasP care rate (c/b)	69%	57%	75%	89%	74%
Last care before exit					
In care not on ART	99 (91%)	148 (96%)	26 (81%)	18 (45%)	291 (87%)
In care on ART	4 (4%)	5 (3%)	1 (3%)	2 (5%)	12 (4%)
In care on ART virally suppressed	6 (5%)	1 (1%)	5 (16%)	20 (50%)	32 (9%)

CHAPTER IV
CONCLUSIONS AND PERSPECTIVES

In this last chapter, we sum up our achievements in conducting this PhD research, raise the main methodological challenges encountered, and present the public health implications and lessons learnt that may be relevant for future research.

As explained in the first chapter of the thesis, there is an unprecedented richness in preventive and curative options now available. Each of them bear specific challenges and outstanding research questions. We thus decided to formalize separately the in-depth discussions of each of the three research themes forming this thesis in the accompanying manuscripts.

4 CONCLUSIONS AND PERSPECTIVES

4.1. Summary of research

The main objective of my PhD was to study the conditions and circumstances of implementation of UTT in sub-Saharan Africa. More specifically, we aimed to characterize and compare the UTT approaches of the five UTT population-level randomized trials in sub-Saharan Africa; to describe the experiences of HCWs on the feasibility and acceptability of UTT; and to describe the individual care trajectories in time, from care referral to viral suppression.

We made several key observations:

- The UTT strategies developed in the five large-scale community-based UTT trials that were launched in the last five years in sub-Saharan Africa present significant disparities, including in terms of study contexts, trial designs and package of health interventions. The underlying characteristics of the trials are likely to affect their findings regarding the feasibility, acceptability, cost-effectiveness and overall impact of their UTT strategies on the HIV epidemic. Our work thus provides foundation for future comparison of trial findings.

- In the rural South African study area of the TasP trial, health care workers assessed home-based HIV services as highly feasible and acceptable among the populations they serve. They emphasized their potential to support UTT strategies as they allow privileged provider-patient relationship that participate in encouraging action in people to access HIV services. Nevertheless, health care workers expressed concerns regarding specific vulnerable populations which are not reached by home-based services, building on the plea for a package of complementary interventions to reach universal care.

- Health care workers were in favour of immediate ART initiation to benefit people's health. Many reported the willingness of patients to initiate ART early in the course of their infection. They nevertheless pointed out that on top of obvious organisational challenges, the large-scale implementation of universal ART would likely be more complex than simply lifting eligibility criteria for ART initiation as asymptomatic patients may struggle more in understanding the rationale of entering a life-long therapy. The evolution of patient's health care expectations will require an adaptation of healthcare providers to ensure the high services coverage required for a UTT strategy to be successful.

- Finally, in the framework of the TasP trial, we observed a high heterogeneity of care trajectories from care referral to viral suppression. Apart from confirming the main features of the leaky cascade, with linkage to care representing the major attrition point, our results highlighted missed opportunities of the health services to retain people in care. A large number of individual care trajectories were shortened, even after several contacts between individuals and health services. This heterogeneity of individuals' behaviours in

response to a universal care strategy calls for a better consideration of one's care utilization patterns to encourage all people to embrace care in the long run.

4.2. Methodological challenges

This PhD was embedded within the TasP trial, which allowed the use of quality data to address our specific research questions regarding UTT implementation: data from all UTT trials in sub-Saharan Africa was collected through a cross-trial collaboration to which the TasP trial took part, quantitative and qualitative data collected cross-sectionnally among HCWs in the TasP trial area and quantitative longitudinal data from TasP trial participants. Nevertheless, the PhD work was challenged by the availability and quality of the data.

- In our first work, direct quantitative comparison of trial's UTT approaches were prevented as there were significant differences in the trials' design and data collection schemes. Besides, no consensual methodology exists yet to allow a standardized and thus validated direct comparison of trials. In response to such challenges, we developed, as a consortium, a simple way to comparatively assess all trials; enabling us to decide which trial components should be compared, and how to interpret their differences across trials in the future, i.e. once all the trials have been fully completed.

- In our second work with health care workers, the main methodological weakness was the cross-sectional design of the study, which did not allow any investigation of possible evolution of health care workers' views throughout the trial. However, we were able to observe that TasP and government health care workers shared similar views on UTT, despite some having experienced it and others not, suggesting a coherence in the opinions of healthcare workers in the area regarding HIV-related issues. Another weakness of the quantitative survey was that, despite the survey being exhaustive, there was only a small number of eligible study participants, preventing any statistical analysis per sub-group or more in-depth analytical analyses. We are currently discussing the opportunity of pooling part of our data with data collected in another UTT trial, the MaxART trial, conducted in neighbouring Swaziland and part of the UT^3C consortium, as both studies have explored health care workers' perceptions regarding universal treatment.

- In our final work with individual care trajectories, the main limitation was that the individuals' care trajectories were constructed on the basis of relatively strong hypotheses, in particular regarding the measure of care status ion local government clinics. Individuals with different care experience may have had similar care stages allocated. To prevent any excessive interpretation, we provided all assumptions in the Methods section of the manuscript. Additionally, as we intended to analyse the links between trajectories and covariates, we gathered trajectories in clusters. Even though those clusters were assessed homogeneous in a statistical point of view, such analysis eclipses the inherent inter-individual variability of the trajectories.

4.3. Public health implications and lessons learnt for future research

Despite the above methodological considerations, the work provided in this PhD documents as best as possible the implementation of a UTT strategy at a large-scale in close-to-real-life settings. Such work arrives in a timely manner as it is now widely acknowledged that diagnosing and treating HIV infection the earliest possible is critical to reduce the burden of HIV in sub-Saharan Africa. The use of the 90-90-90 goals provides a useful framework that can help countries streamline their efforts towards making an AIDS-free world, putting the emphasis to explore more efficient services delivery models [190]. But there is no practical recommendations on how to best use the tools at hand and what additional care modalities are actually needed [191].

Our work participates in the research efforts to provide policy-makers with relevant evidence from which they can build a personalized public health approach, for highest population effect using the available resources, or what some might call “the art of public health” [192].

- The first major observation we made in this PhD work was that there is a panel of interventions that can be used to improve HIV care under the “UTT” banner. The large-scale UTT trials field-tested some of the most effective HIV care interventions in a diversity of settings. Apart from assessing the crude impact of those interventions on the HIV incidence, those trials are a mine of information regarding their feasibility, acceptability and cost-effectiveness of HIV care interventions. The inherent interdisciplinarity of the research led in the framework of those trials brings priceless insights to decision-makers and program planners who face a constantly changing HIV epidemic. Future research will need to focus on characterizing the innovations in the HIV prevention and treatment landscapes, including those which happened while the UTT trials were ongoing (e.g. emergence of PreP as a key biomedical prevention service) [172, 193, 194].

- Secondly, our research raises the voices of those who are at the frontline of service delivery. Health care workers give evidence of how trustful provider-patient relationship, built in an enabling environment such as people’s homes, can make the difference for people accessing care. These findings come at a time when the last decade has highlighted major gaps in the availability, accessibility and quality in the health workforce [186-188]. They participate in calling for more research to assess the potential of task-shifting and the diversification of service delivery platforms outside of the clinic walls to shape the development of a new workforce including community health workers and rationalize healthcare demands [28, 29].

- The last important finding of our research is related to how people behave when they are offered UTT services. We highlighted the heterogeneity of individual care utilization patterns, pointing out the reality of patients cycling in and out of care [30]. Now that countries are rolling out ART for all as a national policy and HIV is transforming into a chronic care condition [195], research needs to focus on how best to tailor HIV care interventions to optimize health outcomes. This includes the development of a more

comprehensive health care offer beyond HIV care that better answers people's care needs [196]. This should also require the development and strengthening of information systems allowing to follow-up one's individual care trajectory [33].

4.4. Place of the PhD work in my personal scientific career

This PhD three-year period confirmed my sincere interest in working towards sustainable public health systems in resource-limiting settings. I had the opportunity to observe the achievements and limits of the TasP trial in improving people's health. Such inspiring framework allowed me to strive for the highest possible data quality and rigorous methods in my own work.

The second lesson that the PhD taught me is how important it is to work within an interdisciplinary team. Cross-fertilization of disciplines appears to me critical when struggling with health and societal issues such as HIV/AIDS.

Finally, I was able to reflect on the multiplicity of roles that I could play as a scientist in today's society. Besides working towards building a research expertise that is relevant for public health matters, I realized how important it is for scientists to take on the responsibility of advocating for health as a right for all, and participate in strengthening the interface between research, policy and society.

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5 REFERENCES

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APPENDICES

The appendices include the following documents :

- Composition of the ANRS 12249 Tasp Study Group (as of October 2017)
- TasP HCP study: quantitative self-administrated questionnaire for TasP nurses
- TasP HCP study: individual interview guide for a nurse working in a Tasp intervention clinic
- TasP HCP study: framework of coding themes for the thematic analysis of the qualitative data

6 APPENDICES

6.1. Composition of the ANRS 12249 Tasp Study Group (as of October 2017)

Table 3: Composition of the ANRS 12249 TasP Study Group (as of October 2017)

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Investigators		
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Coordinators		
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Thembelihle Zuma	Psychology/social sciences	• Africa Health Research Institute, South Africa

6.2. TasP HCP study: quantitative self-administrated questionnaire for TasP nurses

QUESTIONNAIRE FOR
HEALTHCARE PROFFESSIONALS

NURSES – TASP

Date: |___|___|___|___| / |___|___| / |___|___|
Year Month Day

Thank you very much for accepting to participate in this study.

We will ask all the health care professionals working within the TasP research study and working within the Department of Health clinics in the Hlabisa sub-district to respond to this **questionnaire**. The questions you will answer will help us understand **what your job is like**. We are interested in knowing your tasks and responsibilities and how much you are satisfied with your work. The questions will also help us understand **what you think about the activities which increase access to HIV testing, HIV care and HIV treatment**.
We value your opinion about the specific health services that are provided to the people in this community that are participating in the TasP research study.

The questionnaire will take you approximately **30 minutes to complete**.

Each questionnaire is strictly **anonymous**. A unique identification number is used for each questionnaire. Thus, all your answers will be **confidential** and only used for research purposes.

There are no wrong or right answers.

When you have completed the questionnaire, please **return it to the dedicated "HCP study" box.**

The research team would like to thank you for participating in this research that we hope will improve the health services in the community.

Mélanie, Delphine, Sylvie and Joanna, for the TasP team

PART 1.
Who are you?

1.1. General information

What is your age? Please write your birth date and/or your age in years.

|___|___|___|___| / |___|___| / |___|___| AND/OR: Age : |___|___| years

Year Month Day

What is your gender?

Male……. 1
Female……. 2

What is the highest level of formal education you have completed in school?

College (Certificate)……. 1
College (Diploma)…… 2
University (Bachelor)……... 3
University (Honors)……. 4
University (Master)……... 5
University (Medical degree)……. 6
University (PhD)……... 7
Other……. 8

1.2. Job position

1.2.1. When did you start working within the TasP trial? |___|___|___|___| / |___|___|
Year Month

In which trial arm have you worked so far?

In the intervention arm only…… 1
In the control arm only…… 2
In both the intervention and control arms…… 3

Have you ever worked in the Department of Health HIV programme?

No…… 1 GO TO 0
Yes…… 2

If yes, where?

In Hlabisa sud-district…. 1
Elsewhere……. 2

PART 2.
What HIV services do you provide in the clinics?

ART initiation

During the last month, have you provided ART initiation?

No……. 1 GO TO 2.1
Yes…… 2

On average, how many patients do you initiate on ART per week? |___|___|

On average, how many people that are eligible for ART are reluctant to initiate ART?

None…… 1
Less than a quarter ……. 2
Between a quarter and a half …….. 3
More than half……. 4

Do you feel that you have sufficient experience and training to properly address the concerns of people who are reluctant to start ART?

No……. 1
Mostly…….. 2
Yes……... 3

2.1. **ART follow-up services**

During the last month, have you been involved in ART follow-up activities?

No…… 1 GO TO 2.2
Yes…….. 2

On average, how many patients already on ART do you see per week? |___|___|

On average, how many patients that you see for ART follow-up were in shortage of ART drugs?

None…… 1
Less than a quarter ……. 2
Between a quarter and a half …….. 3
More than half……. 4

Do you feel that you have sufficient experience and training to properly address the concerns of people who stopped taking ART?

No……. 1
Mostly…….. 2
Yes…… 3

2.2. **Early ART initiation**

During the last month, did you initiate patients with CD4 counts >500 cells/mm^3 on ART?

No…. 1 GO TO 3.1
Yes…. 2

If yes, on average, how many people with CD4 counts >500 cells/mm^3 do you initiate per week?

|___|___|

On average, how many people with CD4 counts >500 cells/mm^3 refuse to initiate ART?

None…… 1
Less than a quarter ……. 2
Between a quarter and a half …….. 3
More than half……. 4

PART 3
What do you think about testing and treating everybody?

Many people do not access HIV care in South Africa, including in the Hlabisa sub-district. To help people access HIV diagnosis and treatment, the TasP research study has implemented several health services in this community since 2012. Yet, other services may also be useful to increase access to HIV care in the Hlabisa sub-district. We would now like to know what you think of all these services.

3.1. **HIV testing**

HIV testing means offering a rapid HIV diagnosis test to a person.

Have you ever been tested for HIV?

No……	1	GO TO 0
Yes……	2	

If yes, when was the last time you got tested for HIV approximatively?

More than two years ago……..	1
One year ago……	2
Six months ago……..……..	3
Less than six months ago…….	4

According to you, how often should a person get an HIV test in this community?

Less than once every 2 years…….	1
Once every two years……	2
Once per year ……...……	3
Every six months…….....	4
More than every six months…….	5

Home-based HIV testing

"Home-based HIV testing" means offering an HIV test to a person in his/her home.

What do you think about these statements?

	Totally agree	Partially agree	Partially disagree	Totally disagree	No opinion
Offering HIV testing in the home is acceptable to people in this community.	1	2	3	4	5
Offering HIV testing to people in their home limits confidentiality.	1	2	3	4	5
Offering HIV testing to people in their home forces people to test.	1	2	3	4	5
HIV testing at home should be combined with the screening for other diseases in this community.	1	2	3	4	5
Campaigns of home-based HIV testing should be organised at least every year in the whole Hlabisa sub-district.	1	2	3	4	5
Campaigns of home-based HIV testing should be organised by the DoH in the whole Hlabisa sub-district.	1	2	3	4	5
Campaigns of home-based HIV testing organised every year by the DoH may not be feasible in the whole Hlabisa sub-district considering the shortage of health human resource.	1	2	3	4	5
Campaigns of home-based HIV testing organised every year in the whole Hlabisa sub-district may be too expensive for the DoH.	1	2	3	4	5

Mobile HIV testing

"Mobile HIV testing" means offering an HIV test to a person in a mobile unit, outside of the infrastructures of the clinics and hospitals (ex: in a van).

What do you think about these statements?

	Totally agree	Partially agree	Partially disagree	Totally disagree	No opinion
Offering HIV testing in mobile units is acceptable to people in this community.	1	2	3	4	5
Mobile HIV testing limits confidentiality.	1	2	3	4	5
Mobile HIV testing should be combined with the screening for other diseases in this community.	1	2	3	4	5
Campaigns of mobile HIV testing should be organised at least every year in the whole Hlabisa sub-district.	1	2	3	4	5
Campaigns of mobile HIV testing should be organised by the DoH in the whole Hlabisa sub-district.	1	2	3	4	5
Campaigns of mobile based HIV testing organised at least every year by the DoH may not be feasible in the whole Hlabisa sub-district considering the shortage of health human resource.	1	2	3	4	5
Campaigns of mobile HIV testing organised at least every year in the whole Hlabisa sub-district may be too expensive for the DoH.	1	2	3	4	5

In your opinion, what are the best places to set-up mobile HIV testing units in this community?

	Totally agree	Partially agree	Partially disagree	Totally disagree	No opinion
Close to the roads or the important crossroads	1	2	3	4	5
Close to the workplaces	1	2	3	4	5
Close to the markets	1	2	3	4	5
Close to a college or a high school	1	2	3	4	5
Close to soccer field	1	2	3	4	5
On the place of a community event	1	2	3	4	5
Close to churches	1	2	3	4	5
Close to bars/taverns	1	2	3	4	5

Access to HIV care

After a positive HIV diagnosis, a person is referred to HIV care. He/She receives an appointment to go to the nearest clinic a few days later. During this clinic appointment, he/she receives the proper care that he/she needs to improve his/her health (assessment of the stage of the infection, advice on how to live, treatment initiation…)

Among the people who learn they are HIV+, some **refuse to go to the clinic and start HIV care**. According to you, what are the main reasons for that?

	Always	Most times	Some times	Rarely	Never	No Opinion
They have difficulty accepting their positive HIV status.	1	2	3	4	5	6
They are afraid that the community will know their HIV status if they are seen in a clinic that provides HIV care.	1	2	3	4	5	6
They don't think that they need care if they don't feel sick.	1	2	3	4	5	6
They live too far from any clinic.	1	2	3	4	5	6
They don't have enough money to pay for transport to the clinic.	1	2	3	4	5	6
They are working (job, school) at the time of the clinic opening hours.	1	2	3	4	5	6
They have family duties at the time of the clinic opening hours.	1	2	3	4	5	6
They have more important priorities than HIV care.	1	2	3	4	5	6
They are reluctant to take antiretroviral drugs.	1	2	3	4	5	6

Automated SMS reminder of first clinic appointment

"Automated SMS reminder of first clinic appointments" are text messages that are automatically sent by phone to the HIV-positive people a few days prior to their first clinic appointment to remind them to go to the clinic.

What do you think about these statements?

	Totally agree	Partially agree	Partially disagree	T di
Sending SMS to remind HIV-positive people of their first clinic appointment is acceptable in this community.	1	2	3	
Sending SMS to remind HIV-positive people of their first clinic appointment may cause a breach of confidentiality in this community.	1	2	3	
Sending SMS to remind HIV-positive people of their first clinic appointment should be implemented in the whole Hlabisa sub-district.	1	2	3	

Personalised counselling and support to help people link to HIV care

"Personalised counselling and support to help people link to HIV care" is intended for a specific group of HIV+ people: the people who have received a clinic appointment but did not visit the clinic after a few weeks. An HIV counsellor will first phone such HIV-positive person and then maybe visit her/him at home or in any other convenient place; once or several times as needed by this person. The HIV counsellor and the HIV-positive person will discuss together to understand why this person is facing problems to go to the clinic and what he/she can do to overcome these problems. The HIV counsellor will try and make sure that this HIV-positive person feels comfortable about going to the clinic to receive HIV care.

What do you think about these statements?

	Totally agree	Partially agree	Partially disagree	Totally disagree	No opinion
Offering personnalised counselling and support for HIV care will be acceptable to people in this community.	1	2	3	4	5
Supporting HIV+ people to go to the clinics by regularly phoning and visiting them may cause a breach of confidentiality in this community.	1	2	3	4	5
Supporting HIV+ people to go to the clinics by regularly phoning and visiting them may be too intrusive in this community.	1	2	3	4	5
Personnalised counselling and support for HIV care should be implemented in the whole Hlabisa sub-district by the DoH.	1	2	3	4	5
Supporting HIV+ people to go to the clinics by regularly phoning and visiting them may not be feasible by the DoH in the whole Hlabisa sub-district considering the shortage of health human resource.	1	2	3	4	5
Supporting HIV+ people to go to the clinics by regularly phoning and visiting them in the whole Hlabisa sub-district may be too expensive for the DoH.	1	2	3	4	5

Home-based antiretroviral treatment (ART) initiation

"Home-based ART initiation" refers to the fact that a nurse comes to the home of an HIV+ person who is eligible for ART to start him/her on ART and accompany him/her during the first 3 months of treatment.

What do you think about these statements?

	Totally agree	Partially agree	Partially disagree
Offering home-based ART initiation will be acceptable to people in this community.	1	2	3
HIV+ people who have physical difficulties to access HIV care in clinics will accept home-based ART initiation in this community.	1	2	3
HIV+ people who have financial difficulties to access HIV care in clinics will accept home-based ART initiation in this community.	1	2	3
HIV+ people who don't feel comfortable to go to the clinics to access HIV care will accept home-based ART initiation in this community.	1	2	3
Home-based ART initiation may cause a breach of confidentiality in this community.	1	2	3
Home-based ART initiation may force people to accept ART in this community.	1	2	3
Home-based ART initiation should be implemented by the DoH in the whole Hlabisa sub-district.	1	2	3
Home-based ART initiation may not be feasible in the whole Hlabisa sub-district considering the shortage of health human resource.	1	2	3
Home-based ART initiation in the whole Hlabisa sub-district may be too expensive for the DoH.	1	2	3

Early antiretroviral treatment (ART) initiation.

"Early ART treatment initiation" means that all HIV+ people are given ART as soon as they are diagnosed with HIV regardless of their CD4 count or the clinical stage of their infection.

What do you think about these statements?

	Totally agree	Partially agree	Partially disagree	Tota disag
Early ART is good for HIV+ people's health even for those with high CD4 counts.	1	2	3	4
Early ART will be accepted by all HIV+ people in this community even if they are asymptomatic.	1	2	3	4
HIV+ people that properly take their treatment are less likely to transmit HIV to their HIV-negative partners.	1	2	3	4
HIV+ people on ART in this community are more likely to engage in risky sexual behaviour if they think that taking ART protects their partners.	1	2	3	4
Early ART to all HIV+ people should be offered by the DoH in the whole Hlabisa sub-district.	1	2	3	4
ART to all HIV+ people regardless of CD4 count may make HIV services simpler for the DoH to organize for health workers in this community.	1	2	3	4
Early ART for all HIV+ people of the community may not be feasible in the whole Hlabisa sub-district considering the shortage of health human resources.	1	2	3	4
Early ART for all HIV+ people of the community may result in recurrent ART shortage in this community.	1	2	3	4
Early ART for all HIV+ people in the whole Hlabisa sub-district may be too expensive for the DoH.	1	2	3	4

HIV care follow-up

HIV-positive people who receive HIV care need to attend the clinic regularly. This follow up is a very important part of HIV care. It ensures that HIV-positive people always receive the best and most appropriate care that they need.

Among the people who have already attended a clinic for HIV care, some **<u>decide to stop going to the clinic to receive HIV care</u>**. According to you, what are the main reasons for that?

	Always	Most times	Some times	Rarely	Never	No Opinion
They are afraid that the community will know their HIV status if they are seen regularly in a clinic that provides HIV care.	1	2	3	4	5	6
They live too far from any clinic.	1	2	3	4	5	6
They moved too far from the clinic they used to visit.	1	2	3	4	5	6
They don't have enough money to pay for transport to the clinic.	1	2	3	4	5	6
They are working (job, school) at the time of the clinic opening hours.	1	2	3	4	5	6
They have family duties at the time of the clinic opening hours.	1	2	3	4	5	6
They have more important priorities than HIV care.	1	2	3	4	5	6
They are tired of taking drugs.	1	2	3	4	5	6
They are tired of having side-effects due to of the treatment.	1	2	3	4	5	6

Automated SMS reminder of <u>follow-up</u> clinic appointments

"Automated SMS reminder of follow-up clinic appointments" are text messages that are automatically sent by phone to the HIV+ people a few days prior to their next clinic appointment to remind them of their appointment.

What do you think about these statements?

	Totally agree	Partially agree	Partially disagree
Sending SMS to remind HIV-positive people of their <u>follow-up</u> clinic appointment is acceptable in this community.	1	2	3
Sending SMS to remind HIV-positive people of their follow-up clinic appointment may cause a breach of confidentiality in this community.	1	2	3
Sending SMS to remind HIV-positive people of their follow-up clinic appointment should be implemented in the whole Hlabisa sub-district.	1	2	3

PART 4
What do you think about your job?

4.1. **Job satisfaction**

The following questions are about how happy you are with your current job position. Please remember that all your answers will be treated as highly confidential. We will not pass any of your answers to your supervisors.

Thinking specifically about your current job, do you agree with the following?

	Totally agree	Partially agree	Partially disagree	Totally disagree	No opinion
I find real enjoyment in my job	1	2	3	4	5
I like my job better than the average person	1	2	3	4	5
My job needs me to be fit	1	2	3	4	5
Most days I am enthusiastic about my job	1	2	3	4	5
My job is time consuming	1	2	3	4	5
I feel fairly well satisfied with my job	1	2	3	4	5

4.2. **Time pressure**

Please indicate if you agree with the following statements:

"During the last one month, …"	Totally agree	Partially agree	Partially disagree	Totally disagree	No opinion
I could have provided better services to HIV+ individuals if I had had more time for them.	1	2	3	4	5
I could have easily dealt with a significantly higher number of HIV+ individuals.	1	2	3	4	5
I was able to spend as much time with HIV+ individuals as was necessary.	1	2	3	4	5
I have generally had enough time to answer all HIV+ individuals questions and concerns.	1	2	3	4	5
I have been so stressed that I was sometimes impolite to HIV-positive individuals.	1	2	3	4	5
I feel that HIV-positive individuals were probably dissatisfied with the services I provided because I was so rushed.	1	2	3	4	5

Overall, how would you rate the amount of work you have to do every day?

Too high……...	1	Low…….	4
High……..	2	Too low……..	5
Moderate……	3		

4.3. **Self-perceived job performance**

About how many hours altogether did you work in the past 7 days? |___|___|___| hours

4.4. **Individual job-related factors**

To which extent do you agree with the following statements?

	Totally agree	Partially agree	Partially disagree	Totally disagree	No opinion
I usually cope well with changes at work.	1	2	3	4	5
I intend to leave this job as soon as I can find another position.	1	2	3	4	5
I would recommend to my children that they choose a profession in healthcare.	1	2	3	4	5
I am willing to put in a great deal of effort to make the HIV services of my team successful.	1	2	3	4	5
These days I feel motivated to work as hard as I can.	1	2	3	4	5
My profession helps me to achieve my goals in life.	1	2	3	4	5
Overall, I am very satisfied with my work in HIV care.	1	2	3	4	5
I am very satisfied to have a position where one works closely with the community.	1	2	3	4	5
This job gives me a feeling of achievement and accomplishment.	1	2	3	4	5
I am punctual about coming to work.	1	2	3	4	5
I work hard to make sure that no one has to wait a long time before I see him/her.	1	2	3	4	5
I am careful not to make errors at work.	1	2	3	4	5
When I am not sure how to treat a patient's condition I look for information or ask for advice.	1	2	3	4	5
I try to get on well with the other health staff because it makes the work run more smoothly.	1	2	3	4	5
I get along well with my superiors at work.	1	2	3	4	5

4.5. **Perception of the quality of care delivered:**

The question is NOT about the care you have provided yourself. Rather, we would like to know about how you feel the quality of care is within your work environment as a whole.

HIV counseling and testing

During the last month, how would you rate the quality of HIV counseling and testing services provided within your work environment?

Very bad quality of HIV counseling and testing — *Very good quality of HIV counseling and testing*

0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 □

What do you feel could be done to improve the quality of HIV counselling and testing provided within your work environment? *Write 'DK' if you don't know.*

Suggestion 1: _____

Suggestion 2: _____

Suggestion 3: _____

HIV care

During the last month, how would you rate the quality of HIV care services provided within your environment?

Very bad quality of HIV care — *Very good quality of HIV care*

0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 □

What do you feel could be done to improve the quality of HIV care services provided within your work environment? *Write 'DK' if you don't know.*

Suggestion 1:_____

Suggestion 2:

_____

Suggestion 3:

_____

Thank you very much for your effort and time!

Do you have any additional comments or feedback for us?

6.3. TasP HCP study: individual interview guide for a nurse working in a Tasp intervention clinic

INDIVIDUAL INTERVIEW GUIDE
TasP NURSE (INTERVENTION CLINIC)

Presentation of the study

This study aims at describing the perception of the health care professionals regarding HIV services to increase access to HIV testing, access to HIV care and access to HIV treatment.

The first objective of this interview is to better understand your experience regarding the HIV services you offer within the TasP trial. The second objective is to know your perception regarding HIV services aiming at increasing access to HIV care and treatment within the Hlabisa sub-district.

Discussion about ethics, tape-record

This whole session will take no more than 1 hour 30. The discussion will be tape-recorded to facilitate its recollection.

Despite being taped, I would like to assure you that what is said between you and me will strictly be confidential and anonymized, that is to say that your line manager will not know the content of the discussion. What you say will be only used by the researchers for research purposes only, and any information shared will remain anonymous.

You should try to answer and comment as accurately and truthfully as possible.

If there is any question that you do not wish to answer, you do not have to do so; however please try to answer and be as involved as possible.

PRESS THE AUDIO-TAPE ON

PART 1. YOUR EXPERIENCE IN THE TASP TRIAL

First, I would like to discuss with you about your experience within the TasP trial.

As a nurse in a TasP intervention clinic, you have been able to offer ART initiation to all people living with HIV coming to the clinic, and especially to people with high CD4 count.

1. According to you, what are the benefits and risks of early ART for your patients?

- Benefits/Risks in term of health and quality of life

2. When people arrived to your clinic, what did they know regarding the ART eligibility criteria?

- Knowledge of patients regarding the TasP trial when they arrive in the intervention clinic

- Evolution over the course of the trial

3. **What were the main behaviours of your patients regarding ART initiation, especially early ART initiation?**

- Acceptance of ART initiation, Usual/Surprising reactions of people with high CD4 count when they are offered ART initiation
- Reasons for reluctance
- Reasons for changing their mind
- Difference of ART initiation according to their CD4 count
- Evolution over the course of the trial

4. **How did you deal with people reluctant for initiating ART?**

- Management of reluctant person
- Type of counselling the nurse provides according to the CD4 count of the patient
- Evolution over the course of the trial

5. **What were the main behaviours of your patients regarding ART adherence, especially for those who initiate ART with high CD4 count?**

- ART adherence
- Difference of treatment adherence between individuals with high CD4 count and those with lower CD4 count
- Evolution over the course of the trial

6. **How can you explain that a high proportion of people that were identified as HIV+ in the TasP trial did not come to the TasP clinics?**

- Reasons for not going to TasP clinics

7. **How would you qualify your experience in a mobile clinic?**

- Advantages/ disavantages of experience of working in a mobile clinic (comfortable?)
- Challenge to work in a mobile clinic: transportation, infrastructure, drug stock, other equipment
- Impact on the practice?

8. **How did you feel about working in a clinic only dedicated to HIV?**

- Advantages/disavantages of experience of working in a clinic only dedicated to HIV
- Differences compared to a general primary health care clinic?
- Confidentiality issues? Patients comfortable in coming to the TasP clinics?

9. How would you characterize your workload and weekly schedule within the TasP trial?

- Nb of working hours / weekly schedule
- Nb of patients
- Pressure
- Evolution over time

10. In your overall experience in the TasP trial, did you have time to take care of each of your patients?

- Time to take care of each patient, was it sufficient? If no, why?
- Differences according to the clinics
- Activities that counsellors would have liked to do if they had more time
- Evolution over the course of the trial

11. What training have you received to take care of HIV patients in the TasP trial?

- Training received within the trial, was it sufficient?
- Training that the counsellor would have liked to have
- Evolution over time

12. What opportunities have you had to discuss positive and negative job experiences with your line management? Was it useful for your practice?

- Opportunities to discuss experiences with the line management (e.g. regular meeting), was it sufficient?
- Subjects that have been mostly discussed
- Consequence of these discussions in the practice, was it helpful?
- Other opportunities to discuss with line management that the counsellors would have liked to have
- Evolution over time

13. What opportunities have you had to discuss some particular cases with the other health care professionals the TasP trial? With the DoH? Was it useful for your practice?

- Opportunities to discuss experiences with other HCP of the trial (fieldworkers, linkers, counsellors…); with DoH, was it sufficient?
- Subjects that have been mostly discussed
- Consequence of these discussions in the practice, was it helpful?
- Other opportunities to discuss experiences with other HCP of the the TasP trial that the consellors would have liked to have; with DoH?
- Evolution over the course of the trial

PART 2. YOUR PERCEPTION REGARDING EARLY ART INITIATION AND HIV SERVICES TO INCREASE ACCESS TO HIV CARE AND TREATMENT

The first part is finished. I would now be interested in knowing your perception regarding the implementation of ART FOR ALL in the whole Hlabisa sub-district.

14. What do you think of the implementation of ART FOR ALL as a routine service in the Hlabisa sub-district?

- Perception of the implementation of early ART as a routine DoH service
- Reasons for implementation (or not) of early ART (e.g: benefits/risk early ART, organisation of services, simplification of services, frequency of services, costs, human resources, equipment, infrastructures, coordination between HCP)
- Feasibility?

15. How would the health care professionals of the DoH react if ART FOR ALL was implemented routinely in the Hlabisa sub-district?
What role could nurses play in this roll-out?

- Perception of the readiness of DoH HCP for early ART: e.g support from their line management and the local DoH, feeling towards evolving care standards, changes in daily practices and workload
- would they be willing to move forward with early ART? if no, why?
- Role of nurses: e.g take part in the process of implementation, identify the challenges and offer solutions about how to address them

16. How would the community members of the Hlabisa sub-district react if ART FOR ALL was implemented routinely by the DoH?

- Readiness of the community members to implement early ART, would they be willing to move forward with early ART? if no, why?

17. What do you think should be the role of community leaders for the roll-out of ART FOR ALL in the whole Hlabisa sub-district?

- Example of community activities that could help to support immediate ART initiation

18. What do you think should be the role of all health care providers in the community, including traditional healers and herbalists, for the roll-out of ART FOR ALL in the whole Hlabisa sub-district?

- Example of activity that could be provided by health care providers to to support linkage to care activities

To finish the discussion, I would be interested in knowing your perception regarding the services that could be implemented in the Hlabisa sub-district to increase access to HIV care and to HIV treatment.

19. **What do you think about the quality of the HIV testing, HIV care and HIV treatment services offered in Hlabisa sub-district?**

- Coverage *- Diversity of services*

20. **What should be done to help people accessing the clinics and initiate HIV treatment? Which type of HIV services would you like to see implemented in the Hlabisa sub-district?**

- Outreach and clinic-based activities (ex: Phone call, home-visit, home-based ART initiation, SMS reminders, less frequent clinic visit, medication pick up, task shifting, community ART refill group, HIV support group, escort to clinic) *- Necessary conditions for their implementation?*

21. **What do you think about tailoring HIV services to the needs and situations of patients?**

- Adaptation of the services regarding the needs of the patients

22. **How confident are you about the future of HIV care in the Hlabisa sub-district? About patients accessing the care they need?**

23. **In conclusion, how was your experience within the TasP trial?**

PRESS THE AUDIO-TAPE OFF

Comments: Careful. HCP may lead the conversation toward the fact that the TasP trial is ending. Listen to their concerns which are legitimate and relevant. Yet try to always orientate the discussion toward our subjects of interest.

Individual demographic questionnaire to be completed

Please answer the following questions in the spaces provided, circle or tick the most appropriate options.

1. What is your profession:…….

2. Are you: □ Male □ Female

3. How old are you:…… years old

4. Are you originally from the Hlabisa sub-district? Y/N

If no, when did you arrive there?…….

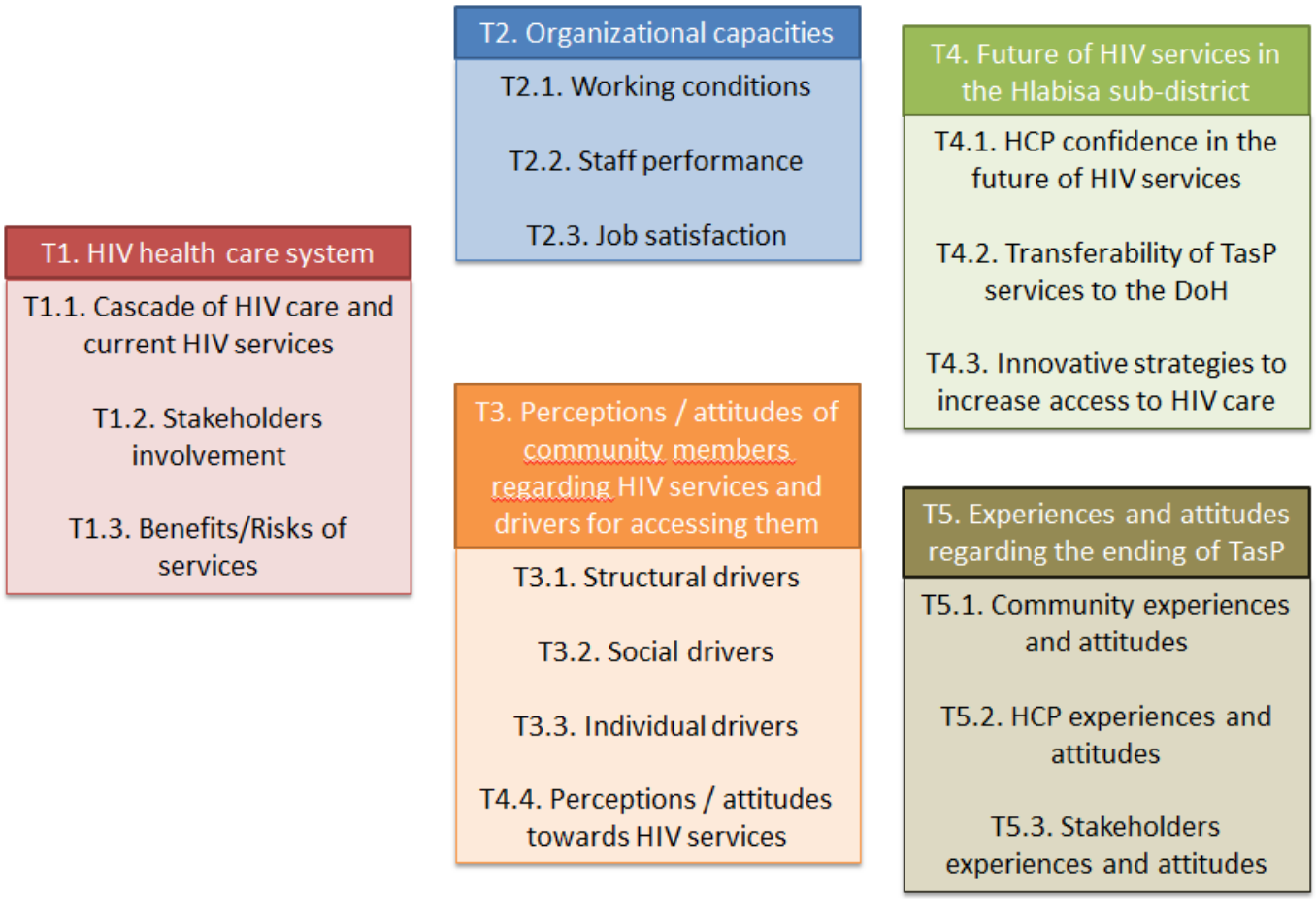
5. For how long have you worked in the TasP trial? …… months

6. What was your previous job?.....

……..

7. How many years of experience do you have in HIV care? ……..

6.4. TasP HCP study: framework of coding themes for the thematic analysis of the qualitative data



T1. HIV health care system (organization of resources to meet the HIV health needs of the community people)	**T1.1. Cascade of HIV care and current HIV services** (strategies currently used to deliver HIV services during the HIV care continuum from HIV testing to viral suppression)	– Community mobilization (strategies currently offered to mobilize community members to take part in HIV services, e.g. *Roadshows, Community meetings, Community dialogues)* – HIV testing (current HIV testing services) o Repeat HIV testing o Home-based HIV testing o Mobile HIV-testing o Clinic-based HIV testing – Linkage to care (first visit to clinic after an HIV test; services currently offered to the people living with HIV to motivate them to access HIV care for the first time) o Phone calls o Home visits – Engagement in care / Retention (staying in care continuously) – ART initiation (starting taking ART for the first time; strategies regarding eligibility for ART initiation) o Evolution of ART guidelines (changes of criteria to initiate ART over time in South African context – DoH) o Early ART (ART initiation regardless of CD4 counts – TasP) – Adherence (taking ART continuously to ensure viral suppression; services currently offered to people living with HIV for them to stay in care and take ART continuously) o Adherence services *(e.g. Tracking: Phone calls, Home visits, ART refill, Support Groups, New technology)*
	T1.2. Stakeholders involvement (people/institution involved in HIV-related work)	– Services providers (actors / institutions which offer HIV care) o DoH ▪ CCGs o TasP o Traditional healers o Private doctors o Funders / Suppliers o NGOs *(e.g. faith based organization)* – Leadership (people / structure / institution / governance / authority who have control, who are involved in the decision making, who are influential) o Community leadership (traditional and civil) o Religious leaders o Government (national, provincial, local) – Community Advisory Board / Group (CAB, CAG: structures that represent the community and advise on the research related issues)
	T1.3. Benefits/Risks of HIV services (appreciation of the HCP regarding the impact of HIV services on the community)	– Benefits (community and individual advantages / positive occurrences associated with / received from the HIV services, *e.g. decrease of opportunistic infections, better health outcomes)* – Risks (community and individual harms / difficulties / vulnerabilities / threats / negative occurrences to which people are exposed with the HIV services), *e.g. drug associated side-effects, stigma)*

T2. Organizational capacities (ability of the organization to deliver HIV services)	**T2.1. Working conditions** (perceptions of the HCP regarding the environment in which they work)	– Logistics (tools of trade and procedures involved to acquire these tools for HCP to perform their tasks) o Transport o Equipment o Working material *(e.g. precise appointment schedule, performance of HIV testing material)* o Wages (remuneration packages) o Staff organization (staff turn-over, working hours, working days, role of each HCP) o Workload (amount of work, patients-HCP ratio) o Staff development / Training (capacity building) – Workplace characteristics (physical features of the workplace) o Internal features of the workplace (*e.g. space to work and to relax, electricity, toilet, water*) o Location of the workplace (where people work; *e.g. where the workplace is situated, distance*) o Occupational safety (health and safety measures at the workplace; *e.g. vaccine given to HCP*) o Security (security within the workplace, security of the equipment, security of the location of the workplace) – Team dynamic / interaction between HCP (inter-relation with other staff members and line management, information sharing)
	T2.2. Staff performance (how HCP carry out / accomplish their work duties)	– Job description (responsibilities and daily practices without specific sentiment) – SOPs (enforcement / application of the SOPs) – Management competences (guidance, support, management styles and skills / capacity, *e.g. fieldworkers who asked for more meeting but it was not accepted*) – Staff competences (aptitude of the staff, skills, knowledge, application of instructions measured in key performance areas / against standards) – Adaptation of practices (modifications / adjustments of HCP practices for services improvement) o Adaptation over time (changes implemented in the practices over time in order to improve the services; *e.g. task allocation among staff members*) o Adaptation according to individuals (tailoring the HIV services to individuals preferences and needs, *e.g. ART refill for Nazareth church community, transport payment for hospital referral*)
	T2.3. Job satisfaction (perceptions of the HCP towards their job / psychosocial well-being of the HCP)	– Positive job satisfaction (positive factors, *e.g. enjoyment for work, fulfilment*) – Negative job satisfaction (negative factors, dislike towards work, *e.g. fear, anger, disappointment, frustration, stress*)

T3. Perceptions and attitudes of community members regarding HIV services and drivers for accessing them (attitudes and perceptions of community members regarding seeking and accessing care, and factors influencing them)	**T3.1. Structural drivers for accessing HIV services** (macro-level/area-level characteristics that could affect individuals accessing HIV care)	– Health system
		  o Waiting times
		  o Range of services offered (*e.g. integrated vs isolated services*)
		  o Quality of services received as customer
		  ▪ Attitudes of HCP (*e.g. attitudes of nurses towards the patients)*
		  ▪ Equipment (*e.g. quality of equipment, shortage of drug)*
		  ▪ Counselling (*e.g. quality of counselling*)
		  o Location of delivery system (*e.g. community-based / distance*)
		  o Confidentiality (*e.g. color of files, different queues*)
		– Migration / Mobility
		– Security in the community (*e.g. fear of collecting ART because of fear of drugs stealing*)
		– Wealth and poverty (*e.g. expenditure, lack of electricity, food security*)

	T3.2. Social drivers for accessing HIV services (community-level characteristics / general conduct and action grounded in social norms and values that could affect individuals accessing HIV care)	– Family dynamics (*e.g. parenting, polygamous family*) – Gender relations / power / roles (*e.g. fear of women to take ART because of their partner, women stay at home*) – Psychosocial support (*e.g. support groups, family / friends support*) – Stigma / Confidentiality issues / Disclosure / Community relation – Knowing other HIV+ individuals *(e.g. family members)* – Cultural beliefs and practices / religion

	T3.3. Individual drivers for accessing HIV services (micro-level / personal characteristics that could affect individuals accessing HIV care)	– Individual behaviors
		  o Awareness / Perception of drugs *(e.g. hopes of efficacy, fear of side-effects)*
		  o Readiness to access HIV care
		  o Denial of HIV-positive status
		  o Self-perceived health status
		  o Drugs and substance abuse (*e.g. alcohol intake*)
		  o Risky sexual practices *(e.g. Multi-partnership)*
		  o Use of traditional care (*e.g. traditional medicine*)
		  o Use of alternative biomedical HIV services (outside of the DoH-TasP care packages) (*e.g. private doctors*)
		  o Demand for more service (*e.g. intervention versus control*)
		  o Other ailments / illness / disease *(e.g. cough, cancer, TB)*
		– Participant profiles
		  o Gender
		  ▪ Men
		  ▪ Women
		  o Age
		  ▪ Young
		  ▪ Old
		  o Profession / Work occupation *(e.g. Truck drivers)*
		  o Education status
		  o People with disabilities

	T3.4. Perceptions and attitudes of community members towards HIV services	– Positive perceptions and attitudes – Negative perceptions and attitudes

T4. Future of HIV services in the Hlabisa sub-district (future prospects regarding the implementation of HIV services to increase access to HIV care within the Hlabisa sub-district)	**T4.1. Transferability of TasP services to the DoH** (perceptions / views / confidence of HCP regarding the relevance, acceptability and feasibility of the DoH implementing / replicating / adapting HIV services developed in the TasP trial)	– Community members' acceptance / Readiness towards HIV services (how the HIV services developed in the TasP trial could be received by the community members) – Operational conditions of implementation (actions suggested at the health system level to ensure that HIV services developed in the TasP trial could be successfully implemented within the DoH) o Workload / Staff organization o Supply of the treatment o Equipment o Community mobilization (*e.g. roadshows*) o Skills of HCP (*e.g. confidence of HCP in their self-efficacy, training, kindness*) o DoH internal characteristics (*e.g. budget*) – Role of stakeholders to implement HIV services (roles of stakeholders *(ex: community leaders, traditional healers)* suggested to ensure that HIV services developed in the TasP trial could be successfully implemented within the DoH)
	T4.2. Innovative strategies to increase access to HIV care (ideas / thoughts / consideration of HCP for novel stakeholders involvement and HIV services that could be implemented by the DoH to increase access to HIV care in the community)	– Partnership between DoH and other stakeholders (collaboration between / complementing contributions from the DoH and stakeholder to increase access to HIV care in the community) o Traditional healers o NGOs o Community leaders – Innovative community-based HIV services (Community-based / Outreach HIV services that are not currently offered in the routine DoH services and that could be implemented to increase access to HIV care in the community; *e.g. home-based, Door-to-door services, Mobile services, Community halls, Organization within the community (e.g. ART refill groups))* – Innovative clinic-based HIV services (HIV services that are not currently offered in the routine DoH services and that could be implemented within the clinics to increase access to HIV care in the community; *e.g. Convenient ART refill (e.g. 3 months refill, ART refill group), Adherence monitoring (e.g. DOT (Directly Observed Treatment))* – Use of new technology / e-health *(e.g. SMS reminders)* – Tailoring of HIV services (adapting HIV services according to individuals preferences and needs) – Integration of HIV services / One-stop-shop (bringing together health services to address multiple conditions) – Incentives (assistance provided that motivate / encourage / support individuals to access HIV care; *e.g. food parcels, transport vouchers*) – Community mobilization (strategies that are not currently offered in the routine DoH services and that could be implemented to mobilize community members to take part in HIV services; *e.g. roadshows, public events*)
	T4.1. HCP confidence in the future of HIV services (perceptions / views / confidence of HCP regarding future prospects for HIV care)	– Positive perceptions – Negative perceptions

T5. Experiences and attitudes regarding the ending of TasP (reactions of people regarding the ending of the TasP trial)	**T5.1. Community experiences and attitudes** (community members reactions towards the ending of the TasP trial services)	– Towards the TasP trial / the Africa Centre – Towards the DoH (*e.g. people will stop taking their ART because they don't want to go to the DoH*)
	T5.2. HCP experiences and attitudes (HCP reactions towards the ending of the TasP trial)	– TasP trial HCP (*e.g. increase of patient volume during the transfer of patients from TasP to the DoH, expectation to be employed by the DoH*) – DoH HCP (*e.g. drastic increase of patient volume in the DoH clinics*)
	T5.3. Stakeholders experiences and attitudes (Stakeholders reactions towards the ending of the TasP trial)	

Intégration et généralisation des stratégies du type "Dépistage et traitement universels du VIH" en Afrique subsaharienne. Exemple de l'essai ANRS 12249 TasP.

Les résultats d'un nombre croissant d'études montrant l'effet préventif du traitement antirétroviral (TARV) sur la transmission du VIH ont jeté les bases de travaux de modélisation suggérant que le dépistage universel et répété du VIH, associé à l'initiation immédiate d'un TARV chez les personnes séropositives, pourraient infléchir l'épidémie de VIH, en particulier en Afrique sub-saharienne. On ne sait pas encore si cette stratégie, qui consiste à *Tester et Traiter Universellement* (TTU), est réalisable au niveau populationnel, compte tenu des contraintes et du niveau requis de prise en charge du VIH qui sont sans précédent.

L'objectif de cette thèse était d'explorer les conditions de mise en œuvre d'une stratégie TTU à large échelle. Sur la base des protocoles d'études communautaires menées en Afrique subsaharienne, nous avons caractérisé la diversité des approches TTU. Dans le cadre de l'une de ces études, l'essai ANRS 12249 TasP mené dans une zone rurale d'Afrique du Sud, nous avons décrit les expériences et perceptions des travailleurs de la santé vis-à-vis de la stratégie TTU et étudié les trajectoires de soins des personnes vivant avec le VIH.

Les résultats rapportés dans cette thèse mettent en évidence que les stratégies TTU englobent une variété d'interventions de prise en charge du VIH, rendant complexe l'évaluation de leur impact sur l'épidémie. Les analyses des opinions des travailleurs de santé et des comportements des patients exposés à une stratégie TTU ont également permis de souligner le potentiel de la stratégie à faire évoluer les pratiques professionnelles et l'accès aux soins des patients. L'ensemble de ce travail permet de mieux appréhender les efforts nécessaires pour assurer un impact maximal d'une stratégie TTU sur la santé des populations en Afrique subsaharienne.

Mots clés : Santé Publique – Epidémiologie sociale – Tester et Traiter universellement – VIH – Afrique du Sud

Integration and generalization of "Universal Test and Treat" strategies for HIV in sub-Saharan Africa. The ANRS 12249 TasP Trial and beyond.

Increasing evidence of the preventive effect of antiretroviral treatment (ART) on HIV transmission have laid the foundations for mathematical models to suggest that universal and repeated HIV testing, combined with immediate initiation of ART among those diagnosed HIV-positive could curtail the HIV epidemic, especially in sub-Saharan Africa. It is still unknown if this strategy, labelled as "Universal Test and Treat" (UTT), could be workable at population level, given the unprecedented HIV services uptake rates that it requires.

The objective of this thesis was to explore the terms of large-scale UTT implementation. Based on the protocols of community-based trials conducted in sub-Saharan Africa, we characterized the diversity of UTT approaches. Within the framework of one of those studies, the ANRS 12249 TasP trial, conducted in rural South Africa, we described the perceptions of health care workers regarding UTT and studied the care trajectories of people living with HIV from care referral to viral suppression.

The findings reported in this thesis highlight that UTT strategies encompass a variety of health interventions, challenging the assessment of their impact on the HIV epidemic. Analyses of health care workers opinions and patients' behaviours when exposed to UTT underlined the potential of the strategy to change professional practices and patients' access to care. Overall this work provides some insights on the efforts needed to allow the maximal public health impact of UTT in sub-Saharan Africa.

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