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Normandie Université

## THÈSE

**Pour obtenir le diplôme de doctorat**

**Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE**

**Préparée au sein de l'Université de Caen Normandie**

**Importance des caractéristiques individuelles dans la rétention dans le soin, l'observance et l'allègement thérapeutique des personnes vivant avec le VIH**

**Présentée et soutenue par  
Anna FOURNIER**

**Thèse soutenue le 07/09/2021  
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## **Titre : Importance des caractéristiques individuelles dans la rétention dans le soin, l'observance et l'allègement thérapeutique des personnes vivant avec le VIH**

### **RÉSUMÉ**

**Introduction :** Pour de nombreuses personnes vivant avec le VIH (PVVIH), un allègement thérapeutique est envisageable, tandis que pour d'autres un traitement pardonnant les doses manquées est nécessaire, avec parfois une prise en charge renforcée pour éviter une interruption de soins médicaux (ISM).

Nos objectifs étaient de déterminer l'incidence et les facteurs de risque (FDR) d'ISM dans deux cohortes de PVVIH ; d'étudier la pardonnance de la trithérapie à base de dolutégravir (DTG) par rapport aux régimes antirétroviraux (ARV) plus anciens ; de déterminer les FDR d'échec virologique sous DTG en monothérapie (DTG-m) et d'explorer l'hétérogénéité du risque comparé à une trithérapie classique, en fonction des FDR identifiés.

**Méthodes :** Nous avons estimé l'incidence d'ISM chez 4 796 PVVIH suivies au centre hospitalier universitaire (CHU) Bichat à Paris et chez 989 PVVIH suivies au CHU de Caen, entre janvier 2010 et mai 2016. Les patients furent considérés en ISM s'ils ne recevaient aucuns soins médicaux pendant 18 mois ou plus.

Nous avons constitué une cohorte prospective multicentrique des modèles d'adhésion aux ARV. L'adhésion moyenne (Adh-m) et la durée maximale d'interruption de traitement (ITmax) ont été mesurées prospectivement sur 6 mois à l'aide de piluliers électroniques.

Nous avons réalisé une méta-analyse sur données individuelles des essais cliniques évaluant le DTG-m. La population d'étude était constituée de PVVIH contrôlées sur le plan virologique depuis plus de 6 mois, et suivies pendant 48 semaines. L'échec virologique était défini par deux charges virales > 50 copies/mL avant la semaine 48.

**Résultats :** Le premier travail retrouva un taux d'incidence d'ISM dans la cohorte de Bichat à 2,5 pour 100 personnes-années (p-a ; intervalle de confiance à 95% [IC95%]=2,3-2,7) et dans la cohorte de Caen à 3,0 pour 100 p-a (IC95%=2,6-3,5). Les FDR indépendamment associés à l'ISM similaires entre les cohortes de Bichat et Caen étaient un délai avant la prise en charge du VIH > 6 mois, et l'absence de traitement ARV. Dans la cohorte de Bichat, ne pas avoir de médecin traitant et avoir un taux de CD4  $\leq$  350/mm<sup>3</sup> au cours du suivi étaient associés à un plus grand risque d'ISM. Dans la cohorte de Caen, les FDR étaient : ne pas avoir renseigné



d'adresse postale et être co-infecté avec le virus de l'hépatite C. Être âgé de plus de 45 ans était associé à un moindre risque d'ISM *vs.*  $\leq 30$  ans. Enfin, être né en Afrique sub-saharienne était un FDR d'ISM à Caen *vs.* né en France, et un facteur protecteur à Bichat.

Le deuxième travail regroupa 399 PVVIH avec différents ARV en 3<sup>e</sup> agent : DTG (n=102), raltégravir (n=90), inhibiteur de protéase boosté (IPb ; n=107) et inhibiteur non nucléosidique de la transcriptase inverse (INNTI ; n=100). Dans le groupe DTG, l'effet des mesures d'adhésion sur la réplication virale ( $R^2$ ) était marginal (+2 %). Adh-m, ITmax et Adh-m x ITmax augmentaient le  $R^2$  de 54 % et 40 % dans les groupes raltégravir et IPb, respectivement. ITmax augmentait le  $R^2$  de 36 % dans le groupe INNTI. Comparé au groupe DTG, le risque d'échec virologique était significativement augmenté pour les groupes raltégravir, INNTI et IPb chez les PVVIH avec une Adh-m  $\leq 95$  %.

Le troisième travail inclut 416 PVVIH, 101 de l'essai suisse EARLY-SIMPLIFIED, 95 de l'essai hollandais DOMONO, 62 de l'essai espagnol DOLAM et 158 de l'essai français MONCAY. Seize échecs furent retrouvés, tous dans le groupe sous DTG-m. Parmi 272 PVVIH traitées par DTG-m, les facteurs indépendants d'échec virologique étaient le nadir de CD4 < 350 cellules/mm<sup>3</sup>; un délai entre le diagnostic de l'infection VIH et le premier ARV > 90 jours ; un taux d'ADN proviral à l'inclusion  $\geq 2,7 \log/10^6$  PBMCs et la présence d'un signal PCR positif d'ARN VIH plasmatique. Nous avons trouvé que l'échec virologique était expliqué en majeure partie par le niveau d'ADN proviral à l'inclusion ( $I^2=80,2\%$ ) avec une différence de risque de 32% entre le groupe DTG-m et le groupe contrôle, parmi les PVVIH avec un taux d'ADN proviral  $\geq 2,7 \log/10^6$  PBMCs.

**Conclusion :** Le contexte socio-démographique, l'histoire de l'infection VIH, le statut immuno-virologique antérieur et actuel associés à la connaissance du niveau d'observance des PVVIH permettraient de guider le choix thérapeutique et les efforts nécessaires pour améliorer le succès virologique. Ainsi, la prise en charge des PVVIH, renforcée ou allégée, devrait être adaptée aux caractéristiques individuelles.

**Mots-clefs :** interruption de soins médicaux, adhésion au traitement, monothérapie, cohorte hospitalière, VIH

**Title: Importance of individual characteristics in retention in care, adherence and maintenance strategies for people living with HIV**

**ABSTRACT**

**Introduction :** For many people living with HIV (PLWH), treatment simplification is possible, while for others treatment forgiving missed doses is necessary, and sometimes with interventions to avoid medical care interruption (MCI).

We sought to identify HIV-infected patients at risk for MCI in two hospital cohorts ; to study the forgiveness of dolutegravir (DTG)-based therapy compared to older antiretroviral (ARV) ; to determine the risk factors of virological failure (VF) under DTG in monotherapy (DTG-m) and to explore the heterogeneity of the risk as compared to a combined ARV therapy (cART), according to the identified risk factors.

**Methods :** We estimated the incidence of MCI in 4,796 PLWH followed at Bichat University Hospital in Paris and in 989 PLWH followed at Caen University Hospital, between January 2010 and May 2016. MCI was defined as patients not seeking care in or outside the clinic for at least 18 months.

Average adherence (Av-Adh) and treatment interruption (TI) to ARV were prospectively measured over 6 months using electronic drug monitoring in a multicentric prospective cohort of 399 PLWH.

We performed an individual participant data meta-analysis of randomized clinical trials evaluating DTG-m. The study population were virologically controlled for at least 6 months, and followed for 48 weeks. Definition of VF was a confirmed viral load > 50 copies/ml before W48.

**Results :** The incidence rate of MCI in the Bichat cohort was 2.5 per 100 person-years (pa; 95% confidence interval [95% CI] = 2.3-2.7) and in the Caen cohort 3.0 per 100 pa (95% CI = 2.6-3.5). In the two cohorts, MCI was more likely in patients who accessed care >6 months after diagnosis, and who were not on ART. In the Bichat cohort, MCI was also more likely in patients who did not report a primary care physician and when the last CD4 count was  $\leq 350$  / mm<sup>3</sup> during follow-up. In the Caen cohort, not having a mailing address reported and a hepatitis C coinfection were independent risk factors for MCI while being older than 45 years was a protective factor. Finally, being born in sub-Saharan Africa was a risk factor for MCI in Caen and a protective factor in Bichat vs. born in France.

In our second study, 399 PLWH were analyzed with different ARV: DTG (n=102), raltegravir (n=90), boosted protease inhibitor (bPI, n=107), and non-nucleoside reverse transcriptase inhibitor (NNRTI, n=100). In the DTG group, the influence of adherence pattern measures on viral replication ( $R^2$ ) for HIV-RNA levels was marginal (+2%). Av-Adh, TI and Av-Adh x TI increased the  $R^2$  by 54% and 40% in the raltegravir and bPI treatment groups, respectively. TI increased the  $R^2$  by 36% in the NNRTI treatment group. Compared to the DTG group, the risk of VF was significantly increased for the raltegravir, NNRTI and IPb groups in PLWH with m-Adh  $\leq 95\%$ .

In our third study, 416 PLWH were included, 101 from the Swiss EARLY-SIMPLIFIED trial, 95 from the Dutch DOMONO trial, 62 from the Spanish DOLAM trial and 158 from the French MONCAY trial. Sixteen failures occurred, all in the experimental group DTG-m. Among 272 participants under DTG-m, VF were more likely in participants who presented a time before first ART  $\geq 90$  days, a nadir of CD4 T cells  $< 350$ , a detected plasma HIV RNA signal at baseline and a HIV DNA level at baseline  $\geq 2.7/10^6$  PBMCs. The highest risk difference between DTG-m and cART group was found when HIV DNA level was  $\geq 2.7 / 10^6$  PBMCs (32%). The VF risk difference could be explained by HIV DNA level ( $I^2=80.2\%$ ).

**Conclusion :** The socio-demographic context, the history of HIV infection, the previous and current immuno-virological status associated with the level of adherence of PLWH should guide the therapeutic choice and interventions to improve virological success. Thus, PLWH care, reinforced or simplified, must be adapted to individual characteristics.

**Keywords :** medical care interruption, adherence, monotherapy, hospital cohort, HIV

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## LISTE DES ABRÉVIATIONS

Adh-m : adhérence moyenne

ARV : antirétroviraux

ASS : Afrique sub-saharienne

CV : charge virale

DTG-m : dolutégravir en monothérapie

FDR : facteur de risque

HR : hazard ratio

IC 95% : intervalle de confiance à 95%

IED : indice européen de déprivation

INI : inhibiteur de l'intégrase

INNTI : inhibiteur non nucléosidique de la transcriptase inverse

IPb : inhibiteur de protéase boosté

ISM : interruption de soins médicaux

IT : interruption de traitement

ORa : odds ratio ajusté

p-a : patients-année

PBMCs : cellules mononuclées de sang périphérique (peripheral blood mononuclear cells)

PDV : perdu de vue

PE : pilulier électronique

PVVIH : personne vivant avec le VIH

## VALORISATION SCIENTIFIQUE

### Articles publiés

Fournier AL, Yazdanpanah Y, Verdon R, et al., **Incidence of and risk factors for medical care interruption in people living with HIV in recent years.** *PLoS One* 2019 Mar 13;14(3): e0213526.

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### Communication orale

Fournier AL, **Factors associated with virological failure in HIV-1 subjects receiving dolutegravir monotherapy as maintenance therapy: a meta-analysis of individual patients data.** *IAS San Francisco, visioconférence, USA 2020.*

### Communications affichées

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Fournier AL, **Incidence et facteurs associés aux interruptions de soins médicaux dans une cohorte de patients infectés par le VIH.** *JNI Saint-Malo, France 2017.*

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## I. INTRODUCTION

Les objectifs du programme commun des Nations Unies sur le VIH/SIDA sont : 95% des personnes vivant avec le virus de l'immunodéficience humaine (PVVIH) connaissent leur statut, 95% des personnes diagnostiquées bénéficient d'un traitement antirétroviral (ARV), et 95% des personnes sous ARV ont une charge virale (CV) indétectable, d'ici 2030 (1). Pour parvenir au dernier point, l'adhésion au suivi et au traitement de l'infection VIH est cruciale (2–4). Ce lien avec le soin doit être créé dès le diagnostic du VIH et maintenu toute la vie des PVVIH.

### a) La rétention dans le soin

La rétention dans le système de soin est le suivi régulier des patients, essentiel pour surveiller l'état physique et mental des PVVIH, maintenir l'adhésion au traitement ARV, et pour en plus prévenir la transmission du VIH (5). Des consultations rapprochées avec le médecin infectiologue et l'équipe paramédicale sont nécessaires la première année de suivi pour limiter la progression de l'infection par le VIH grâce aux ARV, traiter et/ou prévenir la survenue d'infections opportunistes et obtenir l'adhésion du patient au système de soin. Maintenant que l'infection par le VIH est devenue une infection chronique avec un traitement à vie, le défi est de maintenir, améliorer et faciliter la rétention des PVVIH dans le système de soin. En plus de ces intérêts individuels, la rétention des PVVIH a également un intérêt collectif : informer les patients pour prévenir la contamination tant qu'elle est possible, puis obtenir une CV individuelle indétectable, et ainsi diminuer la transmission du VIH dans la population générale. C'est le principe du « treatment as prevention » (TASP) : traitement comme outil de prévention (6). La prise en charge médicale des PVVIH a aussi pour but de prévenir, dépister et traiter d'autres infections sexuellement transmissibles et les complications non infectieuses liées au VIH (maladies cardio-vasculaires, cancers, effets secondaires des ARV) (7). Ce suivi est nécessaire toute la vie des PVVIH.

Une interruption des soins médicaux (ISM) mène au déficit immunitaire, aux complications

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liées au VIH, jusqu'au décès (8). Dans une étude française de 2009, les patients infectés par le VIH qui étaient perdus de vue (PDV) pendant plus d'un an et qui revenaient dans le système de soin avaient un risque de décès 5,1 (intervalle de confiance à 95% [IC95%]=2,1-12,5) fois plus important que ceux qui avaient un suivi régulier (9). Une adhésion durable du patient au suivi médical est donc primordiale pour un contrôle de son infection à vie. D'autre part, les ISM, par la rupture thérapeutique souvent associée, mènent à l'émergence de résistances aux ARV et à des traitements plus complexes. Les hospitalisations d'urgences, les thérapies nécessaires, et les rendez-vous manqués, évalués entre 25 à 35%, représentent aussi un coût et du temps de travail perdu (3). Sur le plan médical et sociétal, prévenir les ruptures de suivi représente un enjeu de santé publique.

### **b) L'adhésion au traitement**

De nos jours, le traitement ARV avec une efficacité proche de 90% permet une restauration immunitaire suffisante pour obtenir une espérance de vie pour les PVVIH similaire à la population générale (10,11). L'adhésion au traitement ARV représente le plus fort prédicteur de suppression virologique (12,13), d'émergence de résistance aux ARV (14), de progression de la maladie et de décès (15,16). Sous inhibiteurs de protéase (IP) non boostés, une observance presque parfaite était nécessaire pour obtenir une suppression virologique (12). Or pour de nombreuses PVVIH, prendre un traitement tous les jours est difficile. Heureusement, des ARV plus robustes face aux doses manquées, inhibiteurs non nucléosidiques de la transcriptase inverse (INNTI) et IP boosté (IPb), ont conduit à une suppression virologique maintenue à des niveaux modérés d'adhésion (> 80%) pour la plupart des patients (17–20). C'est le concept de pardonance.

En fonction des caractéristiques pharmacocinétiques des ARV, les déterminants essentiels de l'observance pour obtenir une suppression virale sont différents (21–24). Parce que les INNTI sont puissants et ont une très longue demi-vie, une interruption de traitement (IT) prolongée était associée à un échec virologique et importait plus que des doses manquées fréquentes (21). Pour les IPb, la moyenne d'adhésion thérapeutique (Adh-m) était le facteur le plus prédictif de la suppression virologique (24). L'étude de l'adhésion au raltégravir, inhibiteurs de l'intégrase

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(INI) de première génération, a montré l'importance des deux critères, Adh-m et IT, sur le succès virologique (23), en cohérence avec sa faible barrière génétique à la résistance (25).

Étudier en vie réelle la pardonnance aux doses manquées d'ARV permet de prédire la durabilité du régime et le risque d'émergence de résistance en cas d'adhésion suboptimale. Aucune étude n'a spécifiquement investigué les associations d'ARV à base d'INI de seconde génération, bien que largement recommandées (26–28).

### **c) L'allègement thérapeutique**

Grâce à l'observance du suivi et du traitement, la grande majorité des PVVIH ont une CV indétectable, sans complications liées au SIDA et sans transmission possible. Un des défis de la prise en charge médicale des patients chroniques est d'améliorer leur qualité de vie. En effet, au-delà de la charge physique et mentale d'un traitement quotidien, les ARV peuvent être associés à des effets secondaires, des interactions médicamenteuses et des complications à long terme (29,30). Dans le but d'améliorer la tolérance au traitement et aussi de réduire les coûts liés aux soins de santé, plusieurs stratégies de maintenance ont été étudiées parmi lesquelles les monothérapies.

Le dolutégravir (DTG) est un INI de deuxième génération avec une barrière génétique élevée au développement de résistance, une bonne pardonnance aux doses manquées, une prise unique quotidienne avec peu d'effets secondaires et peu d'interactions médicamenteuses (26,31–35). Ces caractéristiques l'ont placé comme un bon candidat à une monothérapie en traitement d'entretien. Malheureusement, la plupart des études évaluant le DTG en monothérapie (DTG-m) ont fourni des résultats décevants. La méta-analyse de Calmy et al. a retrouvé un taux d'échec virologique avec le DTG-m à la semaine 48 de 8,9 % (IC95%=4,7-16,2) parmi deux essais cliniques randomisés (DOMONO (35) et DOLAM (36)) et six études observationnelles (37). Depuis, deux essais contrôlés randomisés supplémentaires évaluant la maintenance par DTG-m ont été publiés, à savoir les essais MONCAY et EARLY-SIMPLIFIED avec également des échecs virologiques significativement plus importants sous DTG-m comparé aux trithérapies classiques (38,39). Ces échecs sont cependant rares et de nombreux participants recevant le DTG-m ont conservé une CV indétectable. La connaissance des facteurs associés à l'échec virologique sous DTG-m permettrait de prédire le risque d'échec virologique à l'ère des

## I. Introduction

bithérapies associant un INI et un INNTI de faible barrière génétique, donc à risque de monothérapie fonctionnelle (26,40–44).

### **d) Objectifs de nos travaux**

Les objectifs de nos travaux étaient :

- d’estimer l’incidence d’ISM et d’identifier les facteurs de risques (FDR) d’ISM au diagnostic et au cours du suivi, dans deux cohortes hospitalières, PVVIH suivies au Centre Hospitalier et Universitaire (CHU) Bichat à Paris et les PVVIH suivies au CHU de Caen ;
- d’étudier les modèles d’adhésion au DTG associés à la réplication virale par rapport aux ARV plus anciens et de comparer le risque de réplication virale au sein de sous-groupes stratifiés par niveau d’adhérence ;
- d’identifier les FDR d’échec virologique sous DTG-m et d’explorer l’hétérogénéité du risque d’échec sous DTG-m par rapport au groupe contrôle, à travers une méta-analyse sur données individuelles.

## II. Étude des facteurs de risque de rupture de suivi

### a) Résumé

L'objectif de notre étude était d'identifier l'incidence et les FDR d'ISM dans deux cohortes de PVVIH.

La première cohorte était composée des patients suivis dans le service de maladies infectieuses et tropicales (SMIT) de l'hôpital Bichat à Paris. La deuxième cohorte était constituée des patients suivis dans le SMIT du CHU de Caen. Nous avons utilisé la même méthodologie pour les deux cohortes (définitions, variables recueillies, nettoyage des deux bases de données et analyses statistiques identiques). Seul le logiciel informatique permettant d'enregistrer les données était différent : Nadis® pour le SMIT de Bichat et DMI2 pour Caen, mais les mêmes variables ont pu être extraites.

Nous avons estimé l'incidence d'ISM chez 4 796 PVVIH suivies à l'hôpital Bichat à Paris et chez 989 PVVIH suivies à l'hôpital universitaire de Caen, entre janvier 2010 et mai 2016. Les patients furent considérés en ISM s'ils ne recevaient aucuns soins médicaux pendant 18 mois ou plus.

Le taux d'incidence d'ISM fut estimé dans la cohorte de Bichat à 2,5 pour 100 personnes-années (p-a ; IC95%=2,3-2,7) et dans la cohorte de Caen à 3,0 pour 100 p-a (IC95%=2,6-3,5). Les facteurs associés à l'ISM similaires entre les cohortes de Bichat et Caen étaient un délai avant la prise en charge du VIH > 6 mois (hazard ratio [HR]=1,30; IC95%=1,10–1,54 et HR=1,14; IC95%=1,08-1,21; respectivement), et l'absence de traitement ARV (HR=3,67; IC95%=2,90-4,66 et HR=2,78; IC95%=1,66-4,63). Dans la cohorte de Bichat, ne pas avoir de médecin traitant (HR=2,40; IC95%=2,03–2,84) et avoir un taux de CD4  $\leq$  350/mm<sup>3</sup> au cours du suivi (HR=2,85; IC95%=2,02-4,04 vs. > 500) étaient associés à un plus grand risque d'ISM. Dans la cohorte de Caen, les facteurs associés à l'ISM étaient : ne pas avoir renseigné d'adresse postale (HR=1,73 ; IC95%=1,07-2,80), être co-infecté avec le virus de l'hépatite C (HR=1,76 ; IC95%=1,07-2,88), et être âgé de plus de 45 ans (HR=0,28 ; IC95%=0,15-0,51 vs.  $\leq$  30 ans). Enfin, être né en Afrique sub-saharienne (ASS) était un FDR d'ISM à Caen (HR=2,18 ;

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IC95%=1,42-3,34 vs. né en France), et un facteur protecteur à Bichat (HR=0,75; IC95%=0,62–0,91).

Nos résultats pourraient aider les cliniciens à identifier les patients à risque d'interrompre leur prise en charge et à mettre en place les moyens appropriés plus tôt.

**b) Publication n° 1**



RESEARCH ARTICLE

# Incidence of and risk factors for medical care interruption in people living with HIV in recent years

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## Abstract

### Objectives

With HIV treatment as a prevention strategy, retention in care remains a key for sustained viral suppression. We sought to identify HIV-infected patients at risk for medical care interruption (MCI) in a high-income country.

### Methods

The HIV-infected patients enrolled had to attend the clinic at least twice between January 2010 and October 2014 and were followed up until May 2016. MCI was defined as patients not seeking care in or outside the clinic for at least 18 months, regardless of whether they returned to care after the interruption. The association between MCI and sociodemographic, clinical, and immuno-virological characteristics at HIV diagnosis and during follow-up was assessed using Cox models.

### Results

The incidence rate of MCI was 2.5 per 100 persons-years (95% confidence interval [CI] = 2.3–2.7). MCI was more likely in patients who accessed care >6 months after diagnosis (hazard ratio [HR] = 1.30, 95% CI = 1.10–1.54 vs. ≤6 months) or did not report a primary care physician (HR = 2.40; 95% CI = 2.03–2.84). MCI was less likely in patients born in sub-Saharan Africa (HR = 0.75, 95% CI = 0.62–0.91 vs. born in France). During follow-up, the risk of MCI increased when the last CD4 count was ≤350 (HR = 2.85, 95% CI = 2.02–4.04 vs. >500 cells/mm<sup>3</sup>) and when the patient was not on antiretroviral therapy (HR = 3.67, 95% CI = 2.90–4.66).



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## Conclusions

The incidence of MCI is low in this hospital that serves a large proportion of migrants. Low or no recorded CD4 counts for a medical visit could alert of a higher risk of MCI, even more in patients who accessed HIV care late or did not report a primary care physician.

## Introduction

Antiretroviral treatment (ART) allows people living with HIV (PLHIV) to achieve a life expectancy close to that of the general population [1,2]. The international CASCADE cohort showed a dramatic decrease in mortality rate due to HIV from 40.8 for 1,000 person-years in 1996 to 6.1 in 2004 thanks to the advent of highly active antiretroviral therapy [3]. A French study found AIDS as the cause of death in 2.2 of 1,000 HIV-infected patients during follow-up in 2010 [4]. Now that HIV has become a chronic disease with lifelong treatment, in addition to HIV diagnosis, one of the challenges is to maintain, enhance, and facilitate retention of HIV-infected patients in the care system.

Continuing engagement in care is the key to achieving 95% viral suppression in treated HIV patients by 2025 the third target of UNAIDS in fast-tracking the end of the AIDS epidemic [3,5–7]. At a population level, retention in care and ART adherence, in sustaining an undetectable viral load, limit onwards HIV transmissions, in other words enhance the treatment as prevention (TasP) concept [6,8–11]. At an individual level, medical care interruption (MCI) leads to loss of immunity and complications of HIV infection [10]. In a 2009 French study, HIV-infected patients who interrupted care for more than one year and then came back into care had a risk of death 5-fold higher than regular follow-up PLHIV [7].

Most previous studies highlighted factors collected at the time of HIV diagnosis that were associated with an MCI [12,13], even a few in Northern countries [10,14]. To our knowledge, no study has assessed the risk factors for MCI during the follow-up period. Finding those events that could precipitate patients into an MCI could help physicians spot a difficult time period during follow-up and prevent an MCI. Our aims were to estimate the annual incidence rate of MCI and to identify the risk factors, at the time of diagnosis and during follow-up, of MCI in HIV-infected patients enrolled in a large clinical cohort in Paris from 2010–2016.

## Materials and methods

### Description of the cohort

Patients were part of the HIV clinical cohort of the Infectious Diseases Department of Bichat University Hospital in Paris, France. In addition to inpatient and outpatient services, a desk is dedicated to medical visits without an appointment, and a multidisciplinary support team, including social workers and community NGO staff, works with physicians to support patients in their medical care and administrative procedures. Enrolled patients were  $\geq 18$  years old and had attended the clinic at least twice between January 2010 and October 2014. All the patients enrolled in this study gave their written informed consent to have their medical chart concerning HIV data (sociodemographic, clinical, immunological, virological, and therapeutic) recorded in Nadis, the electronic medical record system designed for medical follow-up of HIV-infected patients. The Nadis database has been declared to the French “commission nationale informatique et liberté” (CNIL, [www.dataids.org](http://www.dataids.org) Fedialis Medica, Marly Le Roi, France, CNIL number: 1171457 May 24th 2006) [15]. No further ethic approval was necessary

according to the French regulation. Electronic medical records were prospectively filled in by medical or paramedical staff at each clinic visit of patients. If an appointment was missed, the patient or the primary care physician if the patient could not be reached was contacted by the infectious diseases referent for information; patient outcomes were recorded as medical summaries in the medical charts. Patients were followed until May 2016.

### Definition of patients with medical care interruption

MCI was deemed to have occurred if patients did not seek care in the infectious diseases clinic or at an outside facility for at least 18 months, regardless of whether they came back into care after the interruption. We chose an 18-month period rather than the 12-month period used in some other studies [13,14,16–18], because French HIV guidelines have moved towards fewer laboratory tests and visits to healthcare centers per year of PLHIV care. The 2013 French guidelines recommend administration of ART to each PLHIV whatever the CD4 count; a once-a-year visit to an infectious disease specialist for patients on ART whose HIV infection has been under control (undetectable viral load and CD4 T cell count >500 cells/mm<sup>3</sup>) for one year without comorbidity; and a clinical and immuno-virological check-up at least every 6 months, which can be performed by the primary care physician [17].

When the calculated time between each visit to the infectious disease clinic exceeded 18 months, the patient's medical record was systematically reviewed. For each case of MCI, we actively searched for any medical contacts or blood tests after the last known visit by reading the medical summaries completed by the attending physicians. Thus, we were able to know if the patients sought care in another department or another hospital, have been followed by another physician outside the hospital, have moved to another region/country, or had died during the period without a visit to the clinic. If a patient came back to care after a presumed MCI with a viral load under 50 copies/mL, we considered that an indication that ART had not been interrupted and that MCI had not occurred, assuming follow-up elsewhere during this period [10].

### Variables

We considered sociodemographic, clinical, immunological, virological, and therapeutic data at HIV diagnosis and during follow-up. We assessed time-dependent variables such as age ( $\leq 30$  years, 31–45 years, and  $> 45$  years), comorbidity (included surgical, medical and psychiatric events), the occurrence of an AIDS indicator condition and viral hepatitis coinfection status, CD4 count, viral load, and ART prescription at each medical visit. If no data were found between day 14 before and day 14 after the medical visit, the time dependent variable(s) were considered to be missing data.

We collected the last mailing address of each patient to document, to determine their distance from the hospital (and assess any difficulties in accessing the facility) and the level of deprivation of the neighborhood [19–21]. Deprivation may influence access and retention in care. The hospital is located in the 18th arrondissement (district) of Paris, one of the poorest areas in the Ile-de-France region, where Paris is situated (Fig 1) [22,23]. Thus, we classified people as living in the 18th arrondissement in Paris, in Paris as a whole (minus the 18th), in the Ile-de-France region (except Paris), and elsewhere or without an available postal code.

### Statistical analyses

We estimated the incidence rate of MCI as the number of patients who had at least one MCI of  $\geq 18$  months, divided by the number of person-years at risk of MCI. Individuals were considered at risk of MCI from the date of enrollment in the study (January 1, 2010 or the date of



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**Fig 1. Geographical area of patients' residence and poverty rates in Ile-de-France.** Among the 4,796 patients participating in the study, 285 lived outside the Ile-de-France region, and no mailing addresses were found for 115 patients. The other patients lived in the Ile-de-France area and were distributed as follows: A. Ile-de-France region, excluding Paris: 2,234 patients where the poverty rate in 2016 was 14%. B. Paris city: 1,610 patients where the poverty rate was 16%; including the 18th arrondissement of Paris: 552 patients where the poverty rate was 24% [22,23].

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first visit in Bichat if they initiated care there at a later date) to their last visit plus 6 months or not later than May 31, 2016, the end-point of the analysis. People who interrupted care were considered from their last visit plus 6 months, when a clinical and immunovirological check-up should have been performed according to French guidelines [17]. Deceased participants were censored at the date of death, if known, or at their last visit plus 3 months. An exact Poisson distribution was used to estimate 95% confidence intervals (CIs). To compare our results with those of other studies, we also estimated the incidence rate of  $MCI \geq 12$  months.

The associations between MCI and sociodemographic, clinical and immuno-virological characteristics at HIV diagnosis and during follow-up were assessed using a Cox model. The proportional hazard assumption was checked using Schoenfeld residuals. The variables which did not respect the proportional hazard assumption were excluded from the model. The variables associated with MCI with a p-value  $< 0.20$  in the univariate analysis were entered into the multivariate model. A backward stepwise regression analysis was used to build the final multivariate model. Variables were considered significant if the Wald test p-value was  $< 0.05$ . Interactions between variables were systematically checked. Statistical analyses were performed using STATA 14 (Stata Corporation, College Station, TX, USA).

## Results

Between January 2010 and October 2014, 4,796 patients had at least two encounters at the Bichat Hospital. Sociodemographic, clinical, biological, and therapeutic characteristics are shown in Table 1. Most were men (63%). Participants were born in France (38%), sub-Saharan Africa (40%), or elsewhere (20%). Heterosexual men and women transmission group represented almost half (48%) of participants: 30% were men who have sex with men (MSM), and 5% were people who inject drugs (PWID).

Sixty-two percent of participants were diagnosed before 2006. At the time of HIV diagnosis, 8% of participants had an AIDS-defining event, 6% an HBV and 6% an HCV co-infection. The

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**Table 1. Characteristics associated with Medical Care Interruption (MCI) at the time of HIV diagnosis of patients seeking HIV care in the infectious diseases department of the Bichat hospital, Paris, between January 2010 and May 2016.**

	All N = 4,796	Regular follow-up (N = 4,179)	MCI ≥18 months (N = 617)
<b>Age at HIV diagnosis (years)</b>			
≤30	1,855 (39%)	1,603 (38%)	252 (41%)
[31–45]	2,275 (47%)	2,004 (48%)	271 (44%)
>45	666 (14%)	572 (14%)	94 (15%)
<b>Year<sup>a</sup> of enrollment in care</b>			
<2002	2,041 (43%)	1,800 (43%)	241 (39%)
[2002–2006[	930 (19%)	797 (19%)	133 (22%)
[2006–2011[	1,064 (22%)	925 (22%)	139 (23%)
[2011–2013[	571 (12%)	494 (12%)	77 (12%)
≥2013	190 (4%)	163 (4%)	27 (4%)
<b>Sex</b>			
Male	3,041 (63%)	2,633 (63%)	408 (66%)
Female	1,755 (37%)	1,546 (37%)	209 (34%)
<b>Country of birth</b>			
France	1,824 (38%)	1,568 (38%)	256 (41%)
Sub-Saharan Africa	1,916 (40%)	1,695 (40%)	221 (36%)
Other countries or unknown <sup>b</sup>	1,056 (22%)	916 (22%)	140 (23%)
<b>Residence</b>			
Ile-de-France	2,234 (46%)	1,978 (47%)	256 (41%)
Paris (except the 18th arr.)	1,610 (34%)	1,393 (33%)	217 (36%)
18th arrondissement of Paris	552 (12%)	471 (11%)	81 (13%)
Other areas	285 (6%)	248 (7%)	37 (6%)
No available postal code	115 (2%)	89 (2%)	26 (4%)
<b>Primary care physician<sup>c</sup></b>			
Yes	3,648 (76%)	2,359 (56%)	283 (46%)
No	1,148 (24%)	1,820 (44%)	334 (54%)
<b>HIV transmission group</b>			
Men who have sex with men	1,462 (31%)	1,290 (31%)	172 (28%)
Heterosexual men and women	2,314 (48%)	2,032 (49%)	282 (46%)
People who inject drugs	257 (5%)	218 (5%)	39 (6%)
Other or no data available <sup>d</sup>	763 (16%)	639 (15%)	124 (20%)
<b>AIDS<sup>e</sup> at HIV diagnosis</b>			
Yes	367 (8%)	326 (8%)	41 (7%)
No	4,429 (92%)	3,853 (92%)	576 (93%)
<b>Hepatitis B coinfection</b>			
Yes	269 (6%)	240 (6%)	29 (5%)
No	4,527 (94%)	3,939 (94%)	588 (95%)
<b>Hepatitis C coinfection</b>			
Yes	269 (6%)	243 (6%)	26 (4%)
No	4,527 (94%)	3,936 (94%)	591 (96%)
<b>HIV viral load at enrollment (copies/mL)<sup>f</sup></b>			
≤1,000	1,294 (27%)	1,114 (27%)	180 (29%)
1,001–10,000	736 (16%)	625 (15%)	111 (18%)
10,001–100,000	1,492 (31%)	1,331 (32%)	161 (26%)
>100,000	1,225 (26%)	1,086 (26%)	139 (23%)

(Continued)

Table 1. (Continued)

	All N = 4,796	Regular follow-up (N = 4,179)	MCI ≥ 18 months (N = 617)
<b>CD4 count at enrollment (cells/mm<sup>3</sup>)</b>			
≤ 350	2,348 (49%)	2,060 (49%)	288 (47%)
> 350	2,448 (51%)	2,119 (51%)	329 (53%)
<b>Time period before first visit<sup>e</sup></b>			
≤ 6 months	3,165 (66%)	2,882 (69%)	368 (60%)
> 6 months	1,631 (34%)	1,382 (31%)	249 (40%)
<b>Time between first visit and first ART<sup>h</sup></b>			
≤ 12 months	2,293 (49%)	2,054 (49%)	239 (39%)
> 12 months	2,359 (51%)	2,053 (49%)	306 (50%)

MCI: Medical Care Interruption

<sup>a</sup>Year of enrolment are presented in classes corresponding to years of different HIV treatment initiation guidelines. In France, it was recommended to initiate ART under 200 CD4/mm<sup>3</sup> in 2002, <350 CD4/mm<sup>3</sup> in 2006; <500 CD4/mm<sup>3</sup> in 2011 and regardless of CD4 count in 2013.

<sup>b</sup>The country of birth was missing for 73 participants

<sup>c</sup>Primary care physician declared by the patient, written in the computer file, to whom medical records from the clinic are sent

<sup>d</sup>The HIV transmission group information was missing for 587 participants

<sup>e</sup>AIDS: acquired immune deficiency syndrome defined by using the CDC classification

<sup>f</sup>The viral load data were missing for 49 participants

<sup>g</sup>Time between HIV diagnosis and first medical visit in or outside the clinic

<sup>h</sup>ART: antiretroviral therapy, prescribed for 4,652 patients by the end of the study period

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median HIV viral load at enrollment in care was 18,900 copies/mL [interquartile range, IQR = 608–105,160]. The median CD4 count at enrollment was 354 cells/mm<sup>3</sup> [IQR = 191–539]. The median time between HIV diagnosis and the first medical contact for HIV was 1.3 months [IQR = 0.2–20] and under 6 months for 66% of individuals. The median time between the first medical visit for HIV and ART initiation was 12.0 months [IQR = 1.9–58.4]. A mailing address was reported by 98% of patients (Fig 1). A referring primary care physician was declared by 76% of patients.

### Identification of medical care interruption

Among the 4,796 patients included, we found 725 patients with a priori no visits in our clinic during at least 18 months and no news at the end-point of the study. Active research highlighted that 68 of them had medical information from another department recorded in their medical records, 65 had died, 167 had moved to another region, and 22 had a primary care physician conduct follow-up for their HIV infection by a primary care physician. Finally, 403 patients were considered to have had at least one MCI and never returned to care (Fig 2).

We also identified 349 patients with no visits to our clinic during at least 18 months but who returned to care during the study period. Among these 349 patients, medical record evaluations showed that 52 patients had medical information recorded during the interruption period; 83 patients came back into care with an undetectable HIV viral load and were considered to have been received follow-up care elsewhere during this time period. Thus, 214 patients had at least one MCI and returned to care.

Overall, 617 of 4,796 (13%) patients had at least one MCI during follow-up and 214 (35%) of them returned to care. Overall, 617 of 4,796 (13%) patients had at least one MCI during follow-up and 214 (35%) of them came back into care.

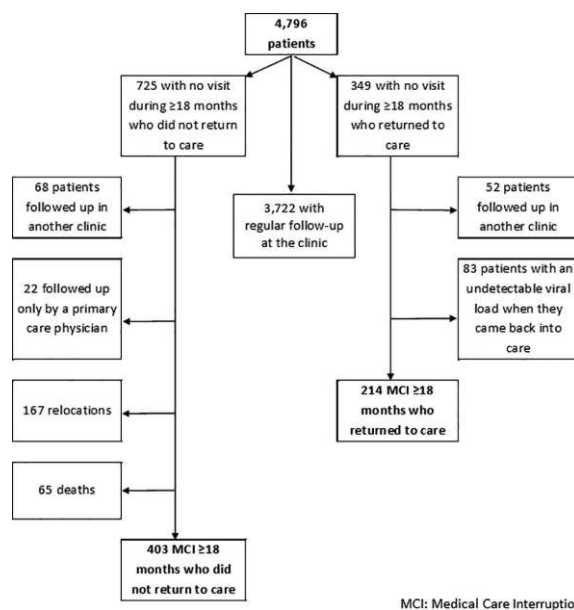


Fig 2. Future of HIV-infected patients with no health care visit for at least 18 months.

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### Incidence of MCI

The 4,796 patients accounted for 24,215 person-years at risk of MCI  $\geq 18$  months. We estimated an incidence rate of having at least one MCI  $\geq 18$  months of 2.5 per 100 person-years [95% CI = 2.3–2.7]. The median duration of follow-up in our study for people who interrupted care was 27.7 months [IQR = 10.5–43.9] vs. 71.3 months [IQR = 49.0–74.7] for those who did not;  $p < 0.001$ . Considering MCI  $\geq 12$  months, we found 874 events among 27,312 person-years, i.e. an incidence rate of 3.2 [95% CI = 3.0–3.5].

### Factors associated with having at least one MCI $\geq 18$ months

Factors associated with having at least one MCI in the univariate analysis are shown in Table 2. A lower risk of MCI was found for people aged between 31 and 45 years at the time of HIV diagnosis (HR = 0.83, 95% CI = 0.70–0.99 vs.  $\leq 30$  years old). People born in sub-Saharan Africa were less likely to have an MCI than were those born in France (HR = 0.79, 95% CI = 0.65–0.95). People living in the 18<sup>th</sup> arrondissement of Paris and in Paris as a whole were more likely at risk of MCI than people living in Ile-de-France (HR = 1.39, 95% CI = 1.08–1.79 and HR = 1.22, 95% CI = 1.02–1.47, respectively). A high risk of MCI was found when any postal code was provided by the patient (HR = 2.08, 95% CI = 1.38–3.15). People who stated that they did not have a primary care physician were more likely to have an MCI (HR = 2.52, 95% CI = 2.14–2.98). A low viral load at the time of HIV diagnosis was associated with a higher risk of MCI (HR = 1.25, 95% CI = 1.00–1.58 for  $\leq 1,000$  and HR = 1.36; 95% CI = 1.05–1.76 for 1,001–10,000 vs.  $> 100,000$  copies/mL). Patients were more likely to have an MCI when they

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**Table 2. Univariate and multivariate analysis of factors associated with Medical Care Interruption (MCI) at the time of HIV diagnosis and during follow-up of patients seeking HIV Care in the infectious diseases department of Bichat hospital, Paris, between January 2010 and May 2016.**

	Hazard ratio <sup>a</sup> (95% CI)	p-value <sup>a</sup>	Adjusted hazard ratio <sup>**</sup> (95% CI)	p-value <sup>**</sup>
<b>Fixed variables</b>				
<b>Age at HIV diagnosis (years)</b>				NS
≤30	1	-		
[31–45]	0.83 (0.70–0.99)	0.04		
>45	1.02 (0.80–1.30)	0.86		
<b>Sex</b>				NS
Male	1.17 (0.99–1.39)	0.06		
Female	1	-		
<b>Country of birth</b>				
France	1	-	1	-
Sub-Saharan Africa	0.79 (0.65–0.95)	0.01	0.75 (0.62–0.91)	0.004
Other countries or data unknown <sup>a</sup>	0.94 (0.76–1.16)	0.55	0.90 (0.73–1.12)	0.35
<b>Residence</b>				
Ile-de-France	1	-	1	-
Paris (except the 18th arr.)	1.22 (1.02–1.47)	0.03	1.20 (0.99–1.46)	0.06
18th arrondissement of Paris	1.39 (1.08–1.79)	0.01	1.38 (1.07–1.78)	0.01
Other area	1.15 (0.81–1.65)	0.44	1.13 (0.79–1.63)	0.50
No available postal code	2.08 (1.38–3.15)	<0.001	2.09 (1.38–3.18)	0.001
<b>Primary care physician<sup>b</sup></b>				
Yes	1	-	1	-
No	2.40 (2.14–2.98)	<0.001	2.40 (2.03–2.84)	<0.001
<b>HIV transmission group</b>				NS
Men who have sex with men	1	-		
Heterosexual men and women	0.96 (0.79–1.17)	0.71		
People who inject drugs	1.24 (0.87–1.78)	0.24		
Other or no data available <sup>c</sup>	1.35 (1.07–1.72)	0.01		
<b>AIDS<sup>d</sup> at HIV diagnosis</b>				NS
Yes	0.79 (0.57–1.1)	0.15		
No	1	-		
<b>Hepatitis B coinfection</b>				
Yes	0.81 (0.56–1.19)	0.27		
No	1	-		
<b>Hepatitis C coinfection</b>				NS
Yes	0.69 (0.45–1.04)	0.06		
No	1	-		
<b>HIV viral load at enrollment (copies/mL)<sup>e</sup></b>				NS
≤1,000	1.25 (1.00–1.58)	0.05		
1,001–10,000	1.36 (1.05–1.76)	0.02		
10,001–100,000	0.96 (0.76–1.21)	0.73		
>100,000	1	-		
<b>CD4 count at enrollment (cells/mm<sup>3</sup>)</b>				NS
≤350	1	-		
>350	1.13 (0.96–1.33)	0.15		
<b>Time period before first visit<sup>f</sup></b>				
≤6 months	1	-	1	-
>6 months	1.34 (1.14–1.58)	<0.001	1.30 (1.10–1.54)	0.003

(Continued)

## II. Étude des facteurs de risque de rupture de suivi

Table 2. (Continued)

	Hazard ratio <sup>a</sup> (95% CI)	p-value <sup>a</sup>	Adjusted hazard ratio <sup>**</sup> (95% CI)	p-value <sup>**</sup>
<b>Time between first visit and first ART<sup>§</sup></b>				NS
≤12 months	1	-		
>12 months	1.18 (0.99–1.41)	0.05		
<b>Time-dependent variables</b>				
<b>Age (years)</b>				
≤30	1	-		
[31–45]	0.87 (0.62–1.21)	0.41		
>45	0.75 (0.54–1.05)	0.10		
<b>CD4 count (cells/mm<sup>3</sup>)</b>				
>500	1	-	1	-
[351–500]	1.39 (0.95–2.04)	0.09	1.42 (1.02–2.08)	0.04
≤350	2.54 (1.80–3.59)	<0.001	2.85 (2.02–4.04)	<0.001
Missing data	4.06 (3.2–5.13)	<0.001	3.87 (3.06–4.89)	<0.001
<b>Antiretroviral therapy</b>				
Yes	1	-	1	-
No	3.52 (2.79–4.45)	<0.001	3.67 (2.90–4.66)	<0.001
<b>AIDS</b>				
Yes	0.91 (0.75–1.11)	0.37		
No	1	-		

MCI: Medical Care Interruption

<sup>a</sup>Hazard ratios and p-values of univariate Cox models carried out for 4,796 patients

<sup>\*\*</sup>Hazard ratios and p-values of the final multivariate Cox model (backward procedure) carried out for 4,796 patients. NS: non-significant (p>0.05)

<sup>a†</sup>The country of birth was missing for 73 participants

<sup>b†</sup>Primary care physician declared by the patient, written in the computer file, to whom medical records from the clinic are sent

<sup>c†</sup>The HIV transmission group information was missing for 587 participants

<sup>d†</sup>AIDS: acquired immune deficiency syndrome defined by using the CDC classification

<sup>e†</sup>The viral load data were missing for 49 participants

<sup>f†</sup>Time between HIV diagnosis and first medical visit in or outside the clinic

<sup>§</sup>ART: antiretroviral therapy, prescribed for 4,652 patients by the end of the study period

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accessed care more than 6 months after the HIV diagnosis (HR = 1.34, 95% CI = 1.14–1.58 vs. presenting within the first 6 months) and when the first ART was prescribed more than one year after the first HIV care visit (HR = 1.18, 95% CI = 0.99–1.41 vs. less than one year).

During follow-up, compared to patients with a CD4 count >500 cells/mm<sup>3</sup>, the risk of MCI increased when the CD4 count was ≤350 cells/mm<sup>3</sup> (HR = 2.54, 95% CI = 1.80–3.59) and when no CD4 count was found in the patients' medical files during the month around the visit (HR = 4.06, 95% CI = 3.20–5.13). People who were not on ART were more likely to have an MCI (HR = 3.52, 95% CI = 2.79–4.45). Comorbidities at HIV diagnosis, health events, and viral load during follow-up did not respect the proportional hazard assumption and were not entered into the multivariate Cox model. Age at HIV diagnosis, sex, AIDS status, hepatitis C coinfection, CD4 count at enrollment and time before first ART were not found to be independently associated with MCI (Table 2). The final multivariate model was carried out using 109,192 visits. At baseline, risk factors found to be independently associated with MCI were living in the 18th arrondissement in Paris (HR = 1.38, 95% CI = 1.07–1.78) or not having an available address (HR = 2.09, 95% CI = 1.38–3.18) vs. living in Ile-de-France outside of Paris,



not indicating a primary care physician (HR = 2.40, 95% CI = 2.03–2.84), and >6 months between diagnosis and the first HIV care visit (HR = 1.30, 95% CI = 1.10–1.54). Factors associated with a lower likelihood of having an MCI were being born in sub-Saharan Africa or in a country other than France (HR = 0.75, 95% CI = 0.62–0.91 and HR = 0.79, 95% CI = 0.63–0.99, respectively vs. born in France). During follow-up, the identified risk factors were having a CD4 count  $\leq 500$  cells/mm<sup>3</sup> with a higher risk of MCI for lower CD4 levels (HR = 1.42, 95% CI = 1.02–2.08 when  $350 < CD4 \leq 500$ ; HR = 2.85, 95% CI = 2.02–4.04 when  $\leq 350$  vs.  $> 500$ ) or missing data for CD4 levels (HR = 3.87, 95% CI = 3.06–4.89), and not being on ART (HR = 3.67, 95% CI = 2.90–4.66).

## Discussion

Among the 4,796 patients who received follow-up for their HIV infection in this French clinical cohort from 2010 to 2016, the incidence rate of having at least one MCI  $\geq 18$  months was estimated at 2.5 per 100 person-years. Patients had an increasing risk of MCI if they lived in the neighborhood surrounding the hospital, were born in France, accessed care more than 6 months after the HIV diagnosis or reported no primary care physician. The risk was also higher if, during follow-up, they did not receive ART and had a CD4 count that was either  $\leq 500$  cells/mm<sup>3</sup> or was not recorded in the electronic medical file.

The incidence of MCI estimated in our study was lower than those estimated in other studies. In France, the estimated incidence rates of MCI are between 3.5 and 17.2 per 100 person-years [10,14,16,24]. The highest rate was in French Guiana, which may be explained by a lack of care settings, precariousness, and HIV stigmatization [24]. Our estimates were lower than the lowest estimates reported to date in France, even if we use the same time definition of MCI (12 months, 3.2 per 100 person-years). Several reasons may explain this difference. First, unlike other studies, we considered that patients had no MCI if they had any contact with care in or outside the hospital vs. only medical visits in the follow-up facility. Second, the comprehensive care management for PLHIV that has been implemented by the Infectious Diseases Department of Bichat Hospital, might facilitate patient retention in care; there are mainly medical visits without appointment, but proactive methods such as text messages or phone calls are used as appointment reminders. Third, the active search for information on patients first assumed to be lost to follow-up reduced the incidence of MCI to a more realistic level, and was the major strength of our study. Because of this approach, we obtained information for 43% of the 1,074 patients first identified with MCI.

The analysis of variables at the time of diagnosis helped characterize patients at risk of MCI. Patients living around the hospital were more likely to have an MCI than those living outside of Paris, suggesting that MCI might be associated with economic deprivation rather than difficulty accessing the hospital. A recent study in Philadelphia found a link between shorter distance to medical care and poor retention [25].

In contrast with all other studies on the topic [14,16,18,24], we found that migrants from sub-Saharan Africa were more likely to be retained in care than patients born in France. For example, Ndiaye et al. [14] found that African patients were at higher risk of interrupting care and not returning (HR = 1.81; 95% CI = 1.16–2.80), than HIV-infected patients born in France. A possible explanation for these opposing results stem from the fact that the Bichat Hospital Infectious Diseases Department has for years treated a large number of immigrants living in the 18th district of Paris or nearby. A high proportion of patients followed for HIV there were born in sub-Saharan Africa, which is much higher than representation in other centers (40% versus 13% in the French HIV national cohort FHDH [18]). The presence of community NGOs in the HIV department and African patients as peer educators to guide and

support other HIV patients may have helped improve retention in care for this population at risk of MCI in the past. Moreover, the French care system provides universal access to care whatever the person's legal status, which limits discrimination regarding origins. Since 1998, migrants have been able to ask for state medical care "AME" and permanence of access to care "PASS" (Art. L. 711-7-1 Public health code) [26]. The role of social workers is very important to help foreigners navigate administrative procedures for obtaining State medical care.

Patients who reported a primary care referent had a lower risk of MCI, and may be an indication of care and concern about their health. Furthermore, an older French study also showed that having a primary care physician is a key to retention in care [14]. The collaboration between infectious diseases and primary care physicians seems crucial for the continuity of care. The automatic sharing of reports between doctors could improve the monitoring of patients [27]. Follow-up of patients at primary care may also reduce some structural barriers related to the hospital, such as transportation access, physician availability, wait time and appointment scheduling [28,29].

We evaluated risk factors of MCI in order to spot these events in the daily follow-up and act to prevent them. Time-dependent ART status was found to be associated with MCI. The treatment represents a link between the care system and the patient [1]. In the UK, people not on ART had a 5-fold higher risk of interrupting care than those on ART [30]. In agreement with other studies, we found an association between low CD4 counts during follow-up and MCI [13,14,18]. Low CD4 counts just before an MCI could be explained, at least in part, by poor adherence to treatment and care. Moreover, we found that patients seen at the clinic without an available CD4 count record had a 4-fold higher risk of MCI than those with CD4 counts >500 cells/mm<sup>3</sup>. We may assume that decreasing CD4 counts or a lack of CD4 measures could be a warning sign of MCI risk.

Our study presented some limitations. First, although we conducted active research of the patients in follow-up, there may remain a misclassification bias of patients wrongly assumed to be lost to follow up. Indeed, we could not consult the incarceration and National Death Index registries. This may have resulted in overestimation of the incidence rate of MCI by wrongly considering these people as having interrupted care. However, in another French study conducted from 1997 to 2006, Ndiaye et al. identified only 2 out of 1,007 patients initially considered lost to follow-up in the National Death Index registry [14]. Second, because we worked with a hospital database, we had no detailed information on the social context (deprivation, life priority needs) or legal status of patients who could be reasons for an MCI. A recent Italian study found that it was more the legal status (in particular undocumented status) than the country of birth that was associated with the risk of MCI [31]. Third, because of the specific recruitment of the hospital situated in a very deprived area with a high proportion of migrants in particular those born in sub-Saharan Africa, we cannot extrapolate our results to other settings. Fourth, the growing literature on rapid ART initiation after HIV diagnosis showed that the retention in care is improved by an early treatment initiation [32]. In our study, we could expect to find an association between an increasing time to treatment and MCI. However, this cross-sectional study evaluated the whole cohort during a time period, and not only newly diagnosed patients, assuming the context and medical practices were important. In return, we observed heterogeneity in terms of years of HIV care initiation. Time to initiate HIV treatment evolved with ART guidelines throughout the period and may explain that the median time between HIV diagnosis and ART initiation was so high (12 months).

In conclusion, we observed a low incidence of MCI in a hospital with a large proportion of very deprived people and of migrants from high HIV-prevalence countries. Low CD4 counts or no recorded CD4 measures for a medical visit could alert the physician of a current high risk of MCI, even more so in patients who accessed care late or did not report a primary care

physician. Our findings may help clinicians identify HIV-infected patients who are at risk of interrupting care and to initiate appropriate interventions earlier for a better retention in care. Further interventions with multidisciplinary HIV care management, involving primary care physicians, could be evaluated to help retain HIV-infected patients in care.

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RESEARCH ARTICLE

## Incidence and risk factors for medical care interruption in people living with HIV in a French provincial city

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### Abstract

#### Objectives

The aim of our study was to identify HIV-positive patients at risk of medical care interruption (MCI) in a provincial city of a high-income country.

#### Methods

We estimated the incidence rate of MCI in 989 individuals followed in an HIV clinic in Caen University Hospital, Normandy, France, between January 2010 and May 2016. We enrolled patients over 18 years old who were seen at the clinic at least twice after HIV diagnosis. Patients were considered to be in MCI if they did not attend care in or outside the clinic for at least 18 months, regardless of whether or not they came back after interruption. We investigated sociodemographic, clinical and immunovirological characteristics at HIV diagnosis and during follow-up through a Cox model analysis.

#### Results

The incidence rate of MCI was estimated to be 3.0 per 100 persons-years (95% confidence interval [CI] = 2.6–3.5). The independent risk factors for MCI were a linkage to care >6 months after HIV diagnosis (hazard ratio [HR] = 1.14; 95% CI = 1.08–1.21), a hepatitis C coinfection (HR = 1.76; 95% CI = 1.07–2.88), being born in Sub-Saharan Africa (HR = 2.18; 95% CI = 1.42–3.34 vs. in France) and not having a mailing address reported in the file (HR = 1.73; 95% CI = 1.07–2.80). During follow-up, the risk of MCI decreased when the patient was older (HR = 0.28; 95% CI = 0.15–0.51 when >45 vs. ≤ 30 years old) and increased when the patient was not on antiretroviral therapy (HR = 2.78; 95% CI = 1.66–4.63).

#### Conclusions

Our findings show that it is important to link HIV-positive individuals to care quickly after diagnosis and initiate antiretroviral therapy as soon as possible to retain them in care.

**Competing interests:** I have read the journal's policy and the authors of this manuscript have the following competing interests: JJP reports grants from Viiv Healthcare and MSD, and personal fees from Gilead, Viiv Healthcare and MSD outside the present work. KC has served as a speaker and as a consultant for Gilead outside the present work. YY has served as a speaker and as a consultant for Abbott, Bristol-Myers Squibb, Gilead, MSD, Roche, Tibotec and Viiv Healthcare outside the present work. RV received travel grants from Gilead, Merck and ViivHealthCare outside the present work. ALF, PF and EP have no conflicts of interest to declare. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

## Introduction

The UNAIDS goals for 2020 were that 90% of all people living with HIV (PLWH) know their HIV status, 90% of all people with diagnosed HIV infection receive sustained antiretroviral therapy (ART), and 90% of all people receiving ART have viral suppression [1]. Continuing engagement in care was the cornerstone of achieving 90% of viral suppression in treated PLWH by 2020 [2–4].

A regular medical follow-up is crucial to monitor the physical and mental condition of PLWH, to maintain ART adherence, and therefore to prevent HIV transmission [5–7]. Thus, improving retention in care of PLWH is a major public health issue with individual and societal outcomes.

Currently, ART is effective and enables CD4 levels to increase enough to achieve a life expectancy for PLWH similar to the general population [8, 9]. Now that HIV has become a chronic disease with lifelong treatment, the challenge is to maintain, enhance, and facilitate retention of HIV-positive patients in the healthcare system.

Medical care interruption (MCI) leads to immunity loss, HIV-related complications, and eventually death [10]. Previous studies have highlighted the risk factors at HIV diagnosis or definitive loss to follow-up [11, 12]. Only a few studies have assessed PLWH at risk of MCI (temporary or definitive) not only at HIV diagnosis but also during the follow-up [10, 13], including a study we performed in a large cohort of PLWH at Bichat university hospital in Paris, with 4,789 patients. We estimated an incidence rate of MCI of 2.5 per 100 persons-years and identified risk factors of MCI [14]. Some results were new, such as patients born in France were more at risk of MCI than those born in sub-Saharan Africa and not having reported a primary care physician found as a risk factor for MCI.

We then conducted the same methodology in a cohort of patients living in a 100,000-inhabitant provincial city in Normandy to estimate incidence rate and risk factors of MCI in a context other than Paris.

## Materials and methods

We used the same methodology as our previous cohort study [14]. Briefly, in a hospital cohort of patients followed for their HIV infection, we retrospectively searched for MCI in the medical file.

### Description of the cohort

Participants come from the HIV clinical cohort of the Infectious diseases department of the Caen university hospital, France. Caen is a 100,000-inhabitant city, located approximately 200 km west of Paris and is the head of southwestern Normandy. PLWH enrolled in this analysis were confirmed to be HIV infected from 1992 to 2014 by western blot, were  $\geq 18$  years old, attended the clinic at least twice between the 1<sup>st</sup> of January 2010 and the 31<sup>st</sup> of October 2014 and gave their informed consent for their medical data to be used in epidemiological analyses. Patients were followed through the 31<sup>st</sup> of May 2016.

### Definition of patients with medical care interruption

Patients were considered in MCI if they did not attend care in or outside the clinic for at least 18 months, regardless of whether or not they came back after interruption. We chose a longer time period than in other studies [12, 13, 15, 16] because French recommendations in 2013 advised one visit a year by an infectious diseases specialist [8]. Times between each contact with the clinic were calculated using the DMI2 computerized file completed by medical or

paramedical employees at each visit at the clinic. When the time between two contacts was over 18 months, the patient's medical record was reviewed to look for hospitalization, other medical contacts or death. For each remaining case of MCI, the patient and if no response, his primary care physician, was contacted by the infectious diseases referent to seek news, any medical contacts or blood tests. Thus, information on hospitalization in another department or another hospital, follow-up by another physician, relocation or death, during the period of no contact with the clinic were collected. If PLWH came back to care after an MCI with an HIV viral load (VL) under 50 copies/mL, we considered that they were still under ART and were not in MCI, assuming they were followed up elsewhere during this period [10].

### Variables

Data were collected prospectively through the DMI2 software for each patient by physicians and other healthcare workers. An electronic form was designed for the HIV follow-up and one file was created for each PLWH followed up at Caen hospital since 1992. For the analysis, we considered variables at HIV diagnosis and during the follow-up.

Clinical data at the time of HIV diagnosis were HIV transmission group (men who have sex with men-MSM, heterosexual, people who inject drug-PWID, or other), presence of Acquired Immune Deficiency Syndrome (AIDS) defined using the CDC classification, hepatitis C virus (HCV) and hepatitis B virus (HBV) coinfections and comorbidities (medical, surgical or psychiatric).

Variables recorded during the follow-up, at each patient visit, were clinical, biological and ART information. We modeled time-dependent age ( $\leq 30$  years, 31–45 years and  $>45$  years), comorbidity, AIDS and coinfections status, CD4 cells and plasma VL, and ART prescription (Y/N).

Finally, we collected the referent physician's contact and the patient's last address if they were declared. The place of residency was used to reflect the distance from the hospital and the level of deprivation of the neighborhood as several studies found an association between MCI, geographical area and precarity [10, 17–19]. We classified people between four geographical areas centered around the clinic: Caen, the hospital city; Calvados, the hospital department; Normandy, the hospital district; outside Normandy; or without address available in the file.

All of the patients enrolled in this study gave their written informed consent to have their medical chart recorded in the electronic medical record system DMI2. The DMI2 database is funded by the French Ministry of Health and obtained a favorable opinion from the French Commission Nationale Informatique et Libertés (CNIL, authorization 1991/27/11) [20]. The ministerial decree authorizes the use of computerized medical and epidemiological records (of those patients who gave their informed consent) by the network of HIV medical centers caring for included patients for the areas of medical follow-up, epidemiological surveys and clinical research.

### Statistical analyses

We estimated the incidence rate of MCI as the number of PLWH who had one or more MCI, divided by the number of person-years at risk of MCI. Individuals were considered at risk of MCI from the date of enrolment in the study (1<sup>st</sup> January 2010 or date of their initial visit at the clinic if subsequent) to their last visit plus 6 months or not later than the 31<sup>st</sup> of May 2016, the end-point. A Poisson's exact distribution was used to estimate 95% confidence intervals (CIs).



We investigated sociodemographic, clinical and immunovirological characteristics at HIV diagnosis and during the time of follow-up through a Cox model to determine associations between MCI and variables.

The variables associated with MCI with a p-value <0.20 in the univariate analysis were entered into the multivariate model. The proportional hazard assumption was assessed using Schoenfeld residuals. We used a backward stepwise regression analysis to build the final multivariate model. Variables were considered significant if the p-value was <0.05 using Wald's test model. The interactions between variables that were significantly associated with MCI were studied two by two.

Statistical analyses were performed using STATA 14 (Stata Corporation, College Station, TX, USA).

## Results

Between the 1<sup>st</sup> of January 2010 and the 31<sup>st</sup> of October 2014, 989 individuals had at least two visits at the HIV department. Median duration of follow-up was 5.6 years [interquartile range (IQR), 2.97–6.08]. The sex ratio was 1.9 with 65% (646/989) men. The median age at enrollment was 45 years [IQR, 37–52]. The proportion of participants born in France was 81% (803/989), in sub-Saharan Africa was 13% (127/989) and in another country was 6% (59/989). A postal address was declared in 90% (894/989) of cases. A referring primary care physician was declared by 54% (539/989) of patients.

Demographic, clinical, biological and ART prescription characteristics at the time of HIV diagnosis are shown in Table 1. Median age was 33 years [IQR, 26–42] at HIV diagnosis. The median time between HIV diagnosis and the first medical contact for HIV was 1.6 months [IQR, 0.4–57.2] and under 6 months for 56% (557/989) of individuals. Half (50%, 493/988) of participants were heterosexual, 33% (324/988) MSM, and 13% (134/988) PWID. Eight percent (77/989) had AIDS at diagnosis, 4% (36/989) had an HBV infection and 10% (99/989) an HCV infection. The median of the first VL available was 11,672 copies/mL [IQR, 68–85,500]. The median of the first CD4 cell count available was 390 cells/mm<sup>3</sup> [IQR, 202–554]. The median time between first medical visit for HIV and the first ART prescription was 28.1 months [IQR, 3.0–85.7].

## Incidence rate of MCI

Among the 989 patients included in the analysis, 284 patients interrupted their medical care for at least 18 months. For 205 patients, there was no visit recorded for 18 months and until the endpoint of the study (Fig 1). The infectious diseases specialist of these patients could be reached and then, the primary care physician for 77% of those declared by patients. Thus, 49 patients had died, 42 had moved to another region, and 5 were followed for HIV by a primary care physician. The infectious diseases specialists contributed to this information for 71% (68/96) and the primary care physicians for 29% (28/96). Finally, 11% (109/989) of patients had an MCI lasting at least until the end point.

In addition, 79 other patients had no visit recorded for  $\geq 18$  months during the follow-up but returned back into care during the study period. After reviewing medical records, 44 patients had an undetectable VL when they returned to care and were considered as followed elsewhere during this time period. Thus, 35 (4%) patients had at least one MCI and returned to care.

Overall, 144 of 989 (15%) patients were considered to have at least one MCI during the follow-up and among them, 35 (24%) returned to care during the study period. We estimated an

**Table 1. Characteristics of people infected with HIV seen at least twice at the infectious diseases department of Caen hospital between January 2010 and March 2014.**

Characteristics	N = 989
<b>Age at HIV diagnosis, years</b>	
Median [interquartile range]	33 [26–42]
<b>Gender, n (%)</b>	
Male	646 (65%)
Female	343 (35%)
<b>Country of birth, n (%)</b>	
France	803 (81%)
Sub-Saharan Africa	127 (13%)
Other countries	59 (6%)
<b>Geographical area<sup>a</sup>, n (%)</b>	
Caen	181 (18%)
Calvados	362 (37%)
Normandie	308 (31%)
Outside Normandie	43 (4%)
No available address	95 (10%)
<b>Primary care physician<sup>b</sup>, n (%)</b>	
Yes	539 (54%)
No	450 (46%)
<b>Time period before first visit<sup>c</sup>, n (%)</b>	
≤ 6 months	557 (56%)
> 6 months	432 (44%)
<b>HIV transmission group, n (%)</b>	
Men who have sex with men	324 (33%)
Heterosexual	493 (50%)
People who inject drug	134 (13%)
Other	37 (4%)
<b>AIDS<sup>d</sup> at diagnosis, n (%)</b>	
Yes	77 (8%)
No	912 (92%)
<b>Hepatitis B coinfection, n (%)</b>	
Yes	36 (4%)
No	953 (96%)
<b>Hepatitis C coinfection, n (%)</b>	
Yes	99 (10%)
No	890 (90%)
<b>First available viral load (copies/mL), n (%)</b>	
<1,000	310 (31%)
1,001–10,000	163 (17%)
10,001–100,000	289 (29%)
>100,000	227 (23%)
<b>First available CD4 cells count (/mm<sup>3</sup>), n (%)</b>	
≤350	443 (45%)
>350	546 (55%)
<b>Time between first visit and first ART<sup>e</sup>, n (%)</b>	
≤12 months	367 (37%)

(Continued)

Table 1. (Continued)

Characteristics	N = 989
>12 months	607 (61%)

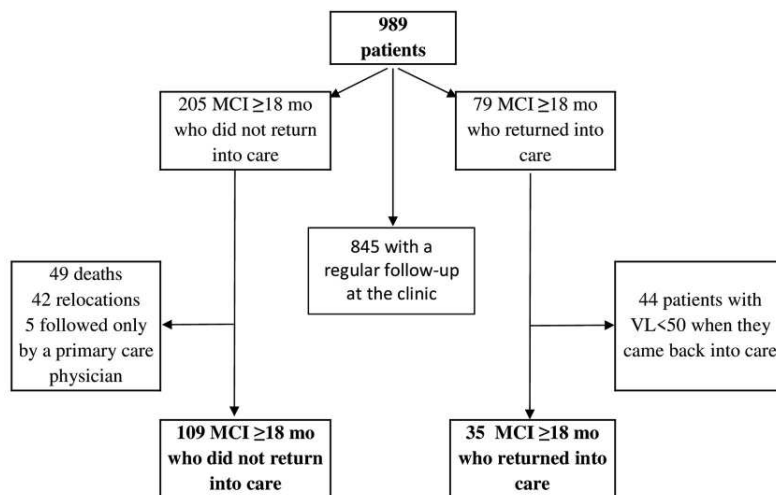
<sup>a</sup>Geographical area: from the address of residency declared by the patient and recorded in the electronic file.  
<sup>b</sup>Primary care physician declared by the patient, and recorded in the electronic file, to whom the specialist letters are sent from the clinic.  
<sup>c</sup>Time between HIV diagnosis and first medical visit in or outside the clinic.  
<sup>d</sup>AIDS: Acquired Immune Deficiency Syndrome defined using the CDC classification.  
<sup>e</sup>Time between HIV first care and first antiretroviral therapy (ART).

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MCI incidence rate of 3.0 per 100 persons-years [95% CI = 2.6–3.5]. The median duration of follow-up in our study for people who interrupted care was 25.2 months [range, 0.2–73.6].

**Risk factors of MCI**

The univariate analysis is shown in Table 2, and the multivariate analysis is shown in Table 3. No significant interactions between variables were found. Risk factors found to be independently associated with MCI were being born in sub-Saharan Africa (SSA; hazard ratio [HR] = 2.18; 95% CI = 1.42–3.34 vs. born in France), not having an available postal address (HR = 1.73; 95% CI = 1.07–2.80), a time before the first medical visit >6 months (HR = 1.14; 95% CI = 1.08–1.21) and an HCV coinfection (HR = 1.76; 95% CI = 1.07–2.88). During the follow-up, patients not under ART were more likely at risk of MCI (HR = 2.78; 95% CI = 1.66–



MCI: Medical Care Interruption

Fig 1. Future of HIV-infected patients with no health care visit for at least 18 months.

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Table 2. Univariate analysis of factors associated with MCI at time of HIV diagnosis and during follow-up in patients at Caen hospital followed between the 1<sup>st</sup> of January 2010 and the 31<sup>st</sup> of May 2016, n = 989 patients.

Factor	Hazard ratio (95% Confidence interval)	p-value
<b>Fixed variables</b>		
Age at HIV diagnosis	0.98 (0.96–0.99)	0.01
<b>Gender</b>		
Male	0.80 (0.57–1.11)	0.19
Female	1	-
<b>Country of birth</b>		
France	1	-
Sub-Saharan Africa	2.51 (1.70–3.71)	<0.0001
Other countries	1.10 (0.51–2.36)	0.82
<b>Available address, n (%)</b>		
Yes	1	-
No	2.30 (1.44–3.66)	0.01
<b>Geographical area<sup>a</sup></b>		
Caen	1	-
Calvados	0.75 (0.48–1.19)	0.22
Normandie	0.73 (0.46–1.19)	0.21
Outside Normandie	1.13 (0.52–2.46)	0.76
Missing data	1.87 (1.07–3.27)	0.03
<b>Primary care physician<sup>b</sup></b>		
Yes	1	-
No	1.32 (0.95–1.83)	0.09
<b>Time period before first visit<sup>c</sup></b>		
≤ 6 months	1	-
> 6 months	1.09 (1.03–1.15)	0.01
<b>HIV transmission group</b>		
Men who have sex with men	1	-
Heterosexual	1.12 (0.77–1.64)	0.54
People who inject drug	1.35 (0.81–2.24)	0.24
Other	0.72 (0.26–2.01)	0.53
<b>Hepatitis B coinfection</b>		
Yes	1.13 (0.46–2.76)	0.79
No	1	-
<b>Hepatitis C coinfection</b>		
Yes	1.68 (1.06–2.67)	0.04
No	1	-
<b>First CD4 cells count (/mm<sup>3</sup>)</b>		
≤350	1	-
>350	1.01 (0.99–1.01)	0.64
<b>Time before first ART<sup>d</sup></b>		
≤12 months	1	-
>12 months	1.17 (0.82–1.66)	0.39
<b>Time-dependent variables</b>		
<b>Age (years)</b>		
≤30	1	-
[31–45]	0.64 (0.37–1.10)	0.11
>45	0.27 (0.15–0.47)	<0.0001

(Continued)

## II. Étude des facteurs de risque de rupture de suivi

Table 2. (Continued)

Factor	Hazard ratio (95% Confidence interval)	p-value
<b>ART</b>		
Yes	1	-
No	2.69 (1.65–4.39)	<0.0001
<b>AIDS<sup>c</sup></b>		
Yes	0.78 (0.51–1.21)	0.27
No	1	-

<sup>a</sup>Geographical area: from the address of residency declared by the patient, and recorded in the computer file.

<sup>b</sup>Primary care physician declared by the patient, written in the computer file, whose consult letters are sent from the clinic.

<sup>c</sup>Time between HIV diagnosis and first medical visit in or outside the clinic.

<sup>d</sup>Time between HIV first care and first antiretroviral therapy (ART).

<sup>e</sup>AIDS: Acquired Immune Deficiency Syndrome defined by using the CDC classification.

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Table 3. Multivariate analysis of factors associated with MCI at time of HIV diagnosis and during follow-up in patients at Caen Hospital followed between the 1<sup>st</sup> of January 2010 and the 31<sup>st</sup> of May 2016, n = 989 patients.

Factor	Hazard ratio (95% Confidence interval)	p-value
<b>Fixed variables</b>		
<b>Country of birth</b>		
France	1	-
Sub-Saharan Africa	2.18 (1.42–3.34)	<0.0001
Other countries	1.02 (0.47–2.21)	0.97
<b>Available address, n (%)</b>		
Yes	1	-
No	1.73 (1.07–2.80)	0.03
<b>Hepatitis C coinfection, n (%)</b>		
Yes	1.76 (1.07–2.88)	0.03
No	1	-
<b>Time period before first visit<sup>a</sup></b>		
≤ 6 months	1	-
> 6 months	1.14 (1.08–1.21)	<0.0001
<b>Time-dependent variables</b>		
<b>Age (years)</b>		
≤ 30	1	-
[31–45]	0.62 (0.35–1.09)	0.09
> 45	0.28 (0.15–0.51)	<0.0001
<b>ART<sup>b</sup></b>		
Yes	1	-
No	2.78 (1.66–4.63)	<0.0001

No additional adjustment.

<sup>a</sup>Time between HIV diagnosis and first medical visit in or outside the clinic.

<sup>b</sup>Antiretroviral therapy prescription (ART).

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4.63). Patients older than 30 years were less likely at risk of MCI (HR = 0.62; 95% CI = 0.35–1.09 when 31–45 vs.  $\leq$  30; and HR = 0.28; 95% CI = 0.15–0.51 when  $>$  45 vs.  $\leq$  30).

## Discussion

Among the 989 PLWH followed in the HIV department in Caen, the incidence rate of having at least one MCI  $>$  18 months was estimated at 3.0 per 100 persons-years from 2010 to 2016. We found that 144 (15%) patients had an MCI, and among them, 109 (11%) were lost to follow-up until the end point of the study and 35 (24%) came back into care during the study period. Independent factors of increasing risk of MCI were being born in SSA, not having declared an available address, time before first medical visit  $>$  6 months after HIV diagnosis and HCV coinfection at HIV diagnosis. During follow-up, no ART was a risk factor for MCI and being older than 30 was a protective factor.

In France, few studies have been conducted to characterize PLWH with MCI. The incidence rate of MCI was estimated to be between 2.5 and 17.2 per 100 persons-years [10, 13–15, 21]. The highest incidence rate was in French Guiana where a lack in healthcare facilities, precarity and stigmatization can explain high MCI rates [21]. In the EuroSIDA cohort, the incidence rate of lost to follow-up ( $>$  12 months and no return to care) was estimated at 3.72 per 100 person-years, which was higher than in our cohort [12]. First, such a difference may be explained by the fact that the definition of MCI was stricter than ours (lost during 12 versus 18 months in our study and only medical visits count versus any contact with care in our study). Second, this study was conducted in different European countries, where care structures and precarity may be higher than in France. For example, Eastern Europe was an independent risk factor for MCI [HR = 1.78; 95% CI = 1.84–2.53].

In addition to the definition, the small number of patients in our clinic allowed for comprehensive care for PLWH, proactive methods to recall appointments and to bring back patients to care by phone calls or text messages that are currently used to secure retention in care. Indeed, patients who do not come to appointments are all actively sought by the infectious diseases specialist himself or a staff member (mail, phone calls).

The active search for patients initially thought to be lost to follow-up is one of the major strengths of our study. We could obtain information for 140 patients (49%) among the 284 ones considered first with an MCI thanks to the help of their infectious diseases specialist and primary care physician. We can underline the high level of answers among primary care physicians (77%) and the robustness of our methodology.

However, we found a higher incidence than in our previous research, which studied an HIV clinic cohort of 4,796 PLWH in Paris [HR = 2.5; 95% CI = 2.3–2.7] [14]. We wonder whether a larger center implements a stronger organization to monitor MCI in a timely manner or if it is an issue of accessibility. This difference could be explained by the distance to the hospital: the Caen clinic covers all of southwestern Normandy, with PLWH living up to 150 km away, compared to the Bichat HIV clinic in Paris, which covers a smaller but more densely populated area with more public transportation facilities. However, we did not find the geographical area of patients as a risk factor for MCI at the Caen clinic. Further studies should investigate whether geographical isolation plays a role in MCI.

Consistent with our findings, several authors have found that people from SSA countries were more likely to be at risk of MCI [13, 15, 16, 21–23]. The authors explained that immigrants are geographically mobile and found a higher proportion of people from sub-Saharan Africa among people with MCI who did not return to care. In another French cohort, Ndiaye et al. [13] found an adjusted HR of 1.81 (95% CI = 1.16–2.80) for these patients to be in MCI. In France, migrants can obtain state medical assistance (AME) and benefit from the

permanence of access to healthcare (PASS) since 1998 (Art. L. 711-7-1 of the Public Health Code) [24]. Even with a healthcare system providing free care for undocumented citizens, this group of PLWH remains more likely at risk of MCI. Interestingly, we found an opposite result in the Paris cohort with a lower risk of MCI among patients born in SSA or in a country other than France (HR = 0.75, 95% CI = 0.62–0.91 and HR = 0.79, 95% CI = 0.63–0.99, respectively) [14]. A higher proportion of people born outside France was followed in this center, which always had a large community of migrants from SSA (40% in the Parisian cohort versus 13% in this provincial one). Moreover, people born in SSA might find more help from the community in Paris and a larger social network, which may not be the case in less densely populated areas, such as Normandy. Further studies are needed to understand this factor with a social approach.

No postal address declared to the clinic was associated with a significantly higher risk of MCI. It is questionable whether patients without an informed address (10%) are homeless or at least housing unstable. Homeless people had a higher risk of MCI among 1,756 PLWH followed in Tourcoing (HR = 2.2, 95% CI = 1.0–4.9) [15].

HCV coinfection at the time of HIV diagnosis was found to be a risk factor. This result was also found by Giordano et al. [23] in a cohort study of 2,619 male US veterans regardless of PWID status.

Being over 30 during follow-up was a protective factor for MCI, and we found a trend for an even lower risk for patients over 45 years old. Young age is indeed often found in the literature as a major risk factor for MCI [10, 13, 15, 25]. The lifestyle of patients  $\leq 30$  years of age, conflictual relationships related to adolescence, and higher stigmatization of the sick individuals are barriers to regular medical follow-up [26]. Improving the retention of the youngest PLWH is an important public health issue, at the individual level by the number of years of life gained and at the collective level by the risk of HIV transmission induced by the sexual activity of people  $\leq 30$  years [27, 28].

Other reasons for MCI listed in the literature include lack of time, fear of stigma, childcare, transportation problems, forgetting the appointment, diseases or other family member's diseases [26]. Multiple visits at the beginning of treatment, before starting treatment, the costs and time of transport, employment restrictions, and family are structural constraints. Our results showed key populations, people born abroad, young individuals, without a postal address available and/or HCV coinfecting, may suffer from these structural constraints but also from a lack of understanding of the disease and care and the need for monitoring.

The same risk factors found to be independently associated with an MCI in our two studies, in a capital or a provincial city, were delayed care initiation after HIV diagnosis and no ART prescribed during follow-up [14]. In the present study, the majority of the patients (54%) initiated ART more than one year after HIV diagnosis. They were diagnosed from 1992 for the oldest patients and included in our study before 2013 guidelines for the majority of our cohort. Indeed, since 2013, French and WHO guidelines are in favor of early antiretroviral initiation, regardless of CD4 count, which suggests that we could expect an improvement in retention in care [1, 8]. The treatment may act as a link between the healthcare system and the PLWH. In the UK, PLWH not on ART had a 5-fold higher risk of interrupting care than those on ART [29]. In addition to benefits of an early linkage to care and ART prescription on patient follow-up, several trials showed improvement in retention in care for a same day treatment, with ART given the day of HIV diagnosis [30–32]. In Haiti, 80% of patients who initiated ART on the day of diagnosis versus 71% of those who did not were still alive and in care at twelve months, and 54% versus 42% with an undetectable VL ( $p = 0.004$ ) [30]. In South Africa, 81% of patients who initiated ART in the rapid arm versus 64% of patients in the standard arm

were retained in care at ten months [31]. In San Francisco, for 4/39 (10%) patients with MCI in the rapid arm versus 7/47 (15%), no significant difference was found [32].

Our study is limited by its retrospective design that may introduce bias in the classification of MCI and other factors due to missing data. Nevertheless, data were collected prospectively in the DMI2<sup>®</sup> database. We actively searched for patients with MCI, which reduced misclassification bias. However, we did not have any information on 13 patients over 144 considered with MCI. We may have overestimated the incidence rate of MCI by considering that dead people have interrupted care.

### Conclusions

Accelerating linkage to care and increasing retention of these key populations in the HIV care continuum is essential to reach the 95-95-95 UNAIDS goals by 2030 to end the epidemic [33]. Interventions to improve retention of PLWH in care should focus on patients identified at risk for MCI as in our study because there are regional differences across cohorts. More studies are needed to identify these differences and barriers PLWH at risk of MCIs struggle with to stay in care. These barriers are structural, behavioral and medical. Reducing the number of visits at the beginning of treatment and the time period before ART initiation are medical hardships. We must consider these issues to tailor optimal interventions.

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**d) Effet de l'indice européen de déprivation sur la rétention dans le soin**

Devant les résultats discordants d'effet du pays de naissance sur le risque d'ISM entre nos deux cohortes, nous avons souhaité étudier davantage la situation socioéconomique des PVVIH suivies. En l'absence de données individuelles, nous avons sollicité l'équipe ANTICIPE (Inserm U1086), pour étudier le niveau de déprivation dans nos deux cohortes et l'effet sur l'ISM.

Un indice européen de déprivation (IED) a été créé dans le but d'évaluer les liens entre la défavorisation des patients et les indicateurs de santé. À partir des données de l'Institut Nationale de la statistique et des études économiques (INSEE) et des données européennes de statistiques sur les revenus et les conditions de vie (EU-SILC), un IED est attribué à chaque îlot regroupé pour l'information statistique (IRIS, groupe d'environ 2000 habitants) et ainsi à chaque adresse postale (45,46). Ainsi, un IED fut attribué à chaque individu via la dernière adresse rentrée dans le dossier au 31 mai 2016. Nous avons réparti les individus de chaque cohorte en quintile du moins défavorisé au plus défavorisé selon les données nationales. Une analyse multivariée des facteurs associés à une ISM dans la cohorte de patients suivis à Bichat et dans celle de Caen furent réalisées avec ce nouvel indice.

Nous avons obtenu 4 742 IED à Bichat et la moyenne de l'IED était 7,51 (-8,59 ; 35,96). Trois quarts (3566 individus) étaient dans le quintile le plus défavorisé soit supérieur à 2,15 (**Tableau 1**). Nous n'avons pas retrouvé d'association significative entre l'IED en analyse univariée (HR=1,00; IC95%=1,00-1,02). Dans la cohorte caennaise, nous avons obtenu 961 IED avec une moyenne de 2,01 (-8,12 ; 19,80). Un tiers (356 individus) était dans le dernier quintile. Nous avons retrouvé une association significative en analyse univariée entre l'IED et l'ISM (HR=1,03; IC95%=1,01-1,06) mais non significative après ajustement sur les autres variables démographiques, cliniques et immuno-virologiques.

## II. Étude des facteurs de risque de rupture de suivi

**Tableau 1. Répartition en quintile de l'indice européen de déprivation dans la cohorte de PVVIH suivies à l'hôpital Bichat et celle suivie au CHU de Caen en fonction de la survenue d'une interruption de soins médicaux.**

	Cohorte de Bichat		Cohorte de Caen	
	Suivi régulier (N = 4137)	ISM ≥18 mois (N = 605)	Suivi régulier (N = 827)	ISM ≥18 mois (N = 134)
<b>IED</b>				
Quintile 1	122 (3%)	18 (3%)	102 (12%)	10 (7%)
Quintile 2	155 (4%)	19 (3%)	99 (12%)	16 (12%)
Quintile 3	249 (6%)	21 (3%)	146 (18%)	20 (15%)
Quintile 4	521 (13%)	71 (12%)	183 (22%)	29 (22%)
Quintile 5	3090 (75%)	476 (79%)	297 (36%)	59 (44%)

*ISM : Interruption de soins médicaux*

*IED : Indice européen de déprivation*

Au final, les deux populations étaient très défavorisées. Nous n'avons pas retrouvé de différence significative d'ISM selon le niveau de déprivation. Les critères socio-économiques liés aux interruptions de soins semblent être individuels et non géographiques.

### **III. Étude de la pardonnance de la trithérapie à base de dolutégravir par rapport aux antirétroviraux plus anciens**

#### **a) Résumé**

L'objectif de notre étude était de déterminer les modèles d'adhésion associés à la réplication virale sous trithérapie à base de DTG par rapport aux ARV plus anciens. Nous avons émis l'hypothèse que le profil pharmacocinétique et la barrière génétique fournis par le DTG permettraient un taux élevé de suppression virologique à des niveaux d'adhésion suboptimale.

Nous avons comparé la cohorte DOLUTECAPS prospective multicentrique de 102 PVVIH recevant une trithérapie comprenant du DTG aux cohortes existantes évaluant le raltégravir, les INNTI et les IPb.

Nous avons mesuré l'Adh-m et la durée maximale d'IT (ITmax) aux ARV prospectivement sur 6 mois à l'aide de piluliers électroniques (PE). Les modèles de régression linéaire multivariée, ajustés sur les facteurs de confusion à l'inclusion, ont exploré l'impact de l'adhésion définie par PE ( $R^2$ ) sur la CV VIH à 6 mois. Des modèles de régression logistique multivariée ont été utilisés pour comparer le risque de réplication virale au sein de sous-groupes stratifiés par niveau d'adhérence, Adh-m basse ( $\leq 95\%$ ) et haute ( $> 95\%$ ).

Trois cent quatre-vingt-dix-neuf PVVIH ont été analysées avec différents ARV : DTG (n=102), raltégravir (n=90), IP boosté (IPb ; n=107) et INNTI (n=100). Dans le groupe DTG, l'effet des mesures d'adhésion sur la réplication virale était marginal (+2 %). Adh-m, ITmax et Adh-m x ITmax augmentaient le  $R^2$  de 54 % et 40 % dans les groupes sous raltégravir et IPb, respectivement. ITmax augmentait le  $R^2$  de 36 % dans le groupe de traitement INNTI. Parmi les PVVIH avec une Adh-m  $\leq 95\%$ , le risque de réplication virale était significativement augmenté pour les groupes : raltégravir (OR ajusté [ORa]=45,6; IC95%=4,5-462,1, p=0,001), INNTI (ORa=24,8; IC95%=2,7-228,4, p=0,005) et IPb (ORa=28,3; IC95%=3,4-239,4, p=0,002) comparé au schéma thérapeutique à base de DTG. Parmi les PVVIH avec une Adh-m  $> 95\%$ , il n'y avait pas de différence significative du risque de réplication virale entre les différents ARV.

### III. Étude de la pardonance de la trithérapie à base de dolutégravir

Ces résultats soutiennent le concept selon lequel le DTG en association avec deux autres ARV actifs permet une meilleure suppression virologique que les ARV plus anciens, raltégravir, l'INNTI et le IPb, chez les PVVIH ayant une adhésion plus faible.

#### **b) Publication n° 3**

#### **Forgiveness of dolutegravir-based triple therapy compared to older antiretroviral regimens : a prospective multicenter cohort of adherence patterns and HIV-RNA replication**

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### III. Étude de la pardonance de la trithérapie à base de dolutégravir

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## ABSTRACT

**Background:** For many people living with HIV (PLWH), taking antiretroviral therapy (ARV) every day is difficult.

**Methods:** Average adherence (Av-Adh) and log-transformed treatment interruption (TI) to ARV were prospectively measured over 6 months using electronic drug monitoring (EDM) in several cohorts of PLWH. Multivariate linear regression models including baseline confounders explored the influence of EDM-defined adherence ( $R^2$ ) on 6-month Log<sub>10</sub> HIV-RNA. Multivariate logistic regression models were used to compare the risk of HIV-RNA detection within subgroups stratified by lower ( $\leq 95\%$ ) and higher ( $>95\%$ ) Av-Adh.

**Results:** Three hundred ninety nine PLWH were analyzed with different ARV: dolutegravir (n=102), raltegravir (n=90), boosted PI (bPI; n=107), and NNRTI (n=100). In the dolutegravir group, the influence of adherence pattern measures on  $R^2$  for HIV-RNA levels was marginal (+2%). Av-Adh, TI and Av-Adh x TI increased the  $R^2$  for HIV-RNA levels by 54% and 40% in the raltegravir and bPI treatment groups, respectively. TI increased the  $R^2$  for HIV-RNA levels by 36% in the NNRTI treatment group. Compared to dolutegravir-based regimen, the risk of VR was significantly increased for: raltegravir (adjusted OR (aOR), 45.6; 95% confidence interval (CI) [4.5 - 462.1],  $p=0.001$ ); NNRTIs (aOR, 24.8; 95% CI [2.7 - 228.4],  $p=0.005$ ) and bPIs (aOR, 28.3; 95%CI [3.4 - 239.4],  $p=0.002$ ) in PLWH with Av-Adh  $\leq 95\%$ . Among PLWH with  $>95\%$  Av-Adh, there were no significant differences on the risk of VR among the different ARV.

## Conclusion

These findings support the concept that dolutegravir in combination with two other



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active ARVs achieves a greater virological suppression than older ARV, including raltegravir, NNRTI and bPI among PLWH with lower adherence.

## INTRODUCTION

Suboptimal adherence to antiretroviral therapy can result in insufficient viral suppression[1,2] and promotes the emergence of drug-resistant viral strains[3]. A landmark study with unboosted protease inhibitors antiretrovirals (ARVs) proposed that more than 95% adherence was required to achieve and maintain virological suppression, which led to the concept that an undetectable HIV viral load (VL) was equivalent to full adherence[1]. Modern antiretroviral therapies with once-daily dosing and low pill burden improved the level of adherence compared to more complex regimens[4,5]. Simpler regimens have improved adherence [4,6] and potent regimens with more favourable pharmacokinetic profiles have allowed more forgiveness to missed doses. Studies investigating non-nucleosides reverse transcriptase inhibitors (NNRTI), boosted protease inhibitors (bPI) and integrase strand-transfer inhibitors (INSTI) as a part of ARV drug combination demonstrated that the minimal level of ARV adherence required to sustain virological suppression may range around 80%.[7,8] However, the methods used to measure adherence, such a self-report or pharmacy refill did not capture treatment interruptions, another independent driver of virological failure[9] and resistance[10]. In addition, these studies did not specifically investigate second-generation INSTI-based ARV combination, although widely recommended.

Real world studies of the ‘forgiveness’ to missed doses of ARV regimen are important, as they may help to predict regimen durability and risk of resistance in a context where suboptimal adherence is probably common[11]. We hypothesised that the pharmacokinetic profile and genetic barrier provided by second-generation INSTI, namely dolutegravir-based ARV combination would allow high rate of virological suppression at low-to-moderate adherence levels. Therefore, we aimed to investigate

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the patterns of adherence to dolutegravir associated with virological replication in comparison to older third agents.

## **METHODS**

### ***Study design and participants***

We conducted an international multicenter prospective cohort study of people living with HIV (PLWH) treated with a dolutegravir-based regimen. The DOLUTECAPS study took place in France and Switzerland, between May 2015 and December 2018. Details of the inclusion criteria are described at the clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT02878642>. Briefly, adults living with HIV starting once or twice-a-day dolutegravir-based regimens were included at the physician's discretion. Because we were interested to cover a large range of different pill taking behaviours, the participation of PLWH perceived by their treating physician at risk of suboptimal adherence was encouraged. Subjects had a genotypic sensitivity score of 3 or more, including dolutegravir. The genotypic sensitivity score represents the total number of ARV drugs in the regimen to which a patient's HIV was susceptible (score, 1), possibly susceptible (score, 0.5), or resistant (score, 0), according to version 30 of the ANRS AC-43 resistance group algorithm (<http://www.hivfrenchresistance.org/2019/tab6.html> ). We did not include people using pillbox organizers and those who were not responsible for taking their antiretroviral pills. Three groups of participants were defined: antiretroviral naïve who initiated dolutegravir (STARTING group); antiretroviral experienced who switched to dolutegravir for virological failure (FAILING group); antiretroviral experienced who switched to dolutegravir while HIV-RNA was suppressed (SWITCHING group).

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Dolutegravir combined with abacavir/lamivudine as a single tablet regimen and multi tablet regimens containing dolutegravir plus at least 2 other active ARVs were allowed. Several centers from our group have incorporated the use of EDM devices in routine practice. In addition, we previously investigated adherence-virological outcome relationships for older ARV such as NNRTI [12], bPI [13,14] and raltegravir [15]. We contrasted the DOLUTECAPS cohort findings with other antiretroviral therapies from our EDM database (Supplemental Figure 1). All participants were followed prospectively with electronic adherence monitoring and an HIV-RNA determination at 6 months as the primary outcome.

#### ***Data collection and adherence pattern measures***

Baseline characteristics including sociodemographic factors and clinical characteristics were collected at baseline for the 4 groups: dolutegravir, raltegravir, bPI and NNRTI. Patients were asked to use electronic drug monitoring (EDM, Aardex, Switzerland) devices to prospectively characterize their pattern of adherence to the third agent for 6 months. The same monitoring strategy and devices were used for the 4 groups. Other ARV pills (for exemple, “backbone nucleos/tide reverse transcriptase inhibitors), if any, were not monitored. Two measures were extracted from electronic dosing history for each participant: 1) the average percent dose adherence corresponding to the number of observed electronic pill cap opening events divided by the expected events; (2) the  $\log_{10}$  transformed duration of the longest treatment interruption (in hours). EDM records were read and reviewed at all study visits, and allowed participants to add any doses taken when they knew they did not use the device. Seventeen participants with no EDM event during the 2 weeks prior month 6 were excluded. This is because non-persistence to any short-acting antiretroviral drug

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is known to be associated with virological replication in most situations.

The Institutional Review Board of the University of Caen, France (which covers all French sites) and the Committee on Human Subjects Research of the University of Lausanne, Switzerland approved all study procedures and the participants provided written informed consent.

#### **Outcomes**

The primary outcome was HIV-1 RNA in plasma measured using the test available in each center with a limit of detection  $\leq 50$  HIV-1 RNA copies/mL plasma. We defined virological replication as a failure to suppress or sustain HIV-RNA to less than 50 copies/mL at 6-month., A value of  $\leq 50$  was imputed to PLWH who had a lower limit of detection above 50 copies/mL for 34 participants in the NNRTI and 56 participants in the bPI treatment groups. Emergence of resistance to dolutegravir and to raltegravir was investigated by genotyping the integrase coding sequence of the virus after the development of virological replication.

#### **Statistical analysis**

Continuous variables were summarized as the mean values, median values, SDs, and interquartile ranges [IQRs] depending on their distributions. Dichotomous data were summarized as numbers and proportions. Regarding baseline and follow-up characteristics, quantitative variables were compared between ARV classes using an analysis of variance or a Kruskal-Wallis test, as appropriate and qualitative variables were compared using Fisher exact test. In order to characterize the adherence pattern associated with HIV-RNA replication, we displayed a three-dimensional scatter plot reporting the level of log HIV-RNA (vertical Z-axis) according to the average adherence

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(horizontal X-axis) and log longest treatment interruption (horizontal Y-axis). Because the original data did not contain enough combinations of x, y, and z values to generate an empirically derived surface plot with <64% average adherence, we censored these observations for data visualization. In addition, we used a smoothing spline interpolation method with  $\lambda=0.1$  as a trade-off between closeness to the original data and smoothness. For each antiretroviral group, we computed three different linear regression models: (i) with average adherence (Model 1); (ii) with treatment interruption (Model 2); (iii) with average adherence, treatment interruption and the product (interaction) of average adherence x treatment interruption (Model 3), as independent covariables with the log HIV-RNA at 6-month as the dependent variable. These models were also adjusted for potential confounders (age, sex, baseline treatment scenarios, i.e naïve, switch or treatment failure, baseline HIV-RNA and CD4-cell count). The influence of the EDM-defined adherence pattern on 6-month HIV-RNA was assessed in two ways: (i) by testing the slope of each adherence pattern parameter coefficient to zero; (ii) by assessing the incremental R-squared value (or variance explained) for each model, compared to a model without EDM adherence measurement (i.e. including only baseline factors).

The effect size of factors associated with the probability of virological detection (HIV-RNA>50 copies/mL) was estimated by calculating odds ratios (ORs) and adjusted OR using univariate and multivariate logistic regression models, respectively. This analysis was performed in the overall cohort and in subgroups with higher (>95%) and lower ( $\leq$ 95%) average adherence[1]. Analyses were performed using PowerView, version 2.3.3 (Aardex Group, Sion, Switzerland) and SAS, version 9.4 (SAS Institute, Cary, NC). All reported P values are 2-sided, and a P value of 0.05 or less denoted statistical significance.

## RESULTS

### ***Baseline characteristics***

The baseline characteristics of the participants are shown in Table 1. Seventy-two percent of the participants treated by dolutegravir-based regimen were men and the mean age was 47.7 years. Approximately, one-quarter of the participants treated by dolutegravir-based regimen were treatment-naive at baseline. Forty-seven (46%) PLWH had a plasma HIV RNA <50 copies/mL at study entry. The median baseline CD4 cell count was 494 (IQR, 290–705), and the median baseline plasma HIV RNA level was 2.1 log<sub>10</sub> (IQR, 1.6-4.1). The baseline characteristics from PLWH treated with other third agents are presented in Table 1. In the NNRTI-based group, the third agent was nevirapine for 70 PLWH, efavirenz for 12 PLWH and rilpivirine for 18 PLWH. In the boosted PI group, the third agent was lopinavir for 54 PLWH, atazanavir for 48 PLWH and other boosted PI for 3 PLWH.

### ***HIV-RNA at month-6***

In the dolutegravir treatment group (Table 2), eight PLWH had low levels of HIV-RNA replication: 5/24 (17%) in the failing group (median HIV-RNA 132 cp/mL, range [88-168]); 2/26 (8%) in the starting group (HIV-RNA 80 and 161 cp/mL) and 1/46 (2%) in the switching group (HIV-RNA 73 cp/mL). Among those, 3/8 were amplified and none demonstrated resistance mutation to the INSTI class. In the raltegravir treatment group (Table 2), 18 PLWH had HIV-RNA replication (median HIV-RNA 362 copies/mL, range [57-51300]) and 14/18 were subjected to nucleic acid amplification and sequencing: 4 samples harboured INSTI conferring resistance to raltegravir (Q148H, N155H, Q148R and Y143A). In the NNRTI treatment group (Table 2), 12 PLWH had HIV-RNA

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replication (median HIV-RNA 854 copies/mL, range [66-15000]). In the bPI group (Table 2), 26 PLWH had HIV-RNA replication (median HIV-RNA 11000 copies/mL, range [59-801400]). No data were available for resistance testing in the bPI and NNRTI groups.

#### ***Adherence pattern and HIV-RNA relationships***

Figure 1 displays the 6 months Log<sub>10</sub> HIV-RNA according to the EDM-defined adherence pattern by antiretroviral regimen among 399 PLWH. As shown in Figure 2A, the surface plot for dolutegravir-based triple therapy is flat, indicating a low level of HIV-RNA replication regardless of the adherence pattern. None of the models including adherence pattern parameters was significantly associated with 6-month HIV—RNA level (Figure 2A) and the incremental HIV-RNA variance explained by the inclusion of adherence pattern variables was minimal (2%). In contrast, the adherence patterns were significantly associated with the level of virological replication above the detection threshold for all older ARV, with an incremental variance explained ( $R^2$ ) ranging from 14% (Figure 2D, model 2) to 54% (Figure 2B, model 3). The model 3 had the highest HIV-RNA level variance explained for the raltegravir group (Figure 2B) and the bPI group (Figure 2D), suggesting that the influence of one adherence measure depends on the value of the other. Regarding the NNRTI group (Figure 2C), the longer treatment interruption (model 2) had the highest variance explained to predict HIV-RNA level.

#### ***Predictors of HIV-RNA > 50 copies/mL***

In the overall cohort, factors associated with virological detection (i.e. probability of 6-month HIV-RNA > 50 copies/mL) in the univariate and multivariate analyses are shown in Table 2.



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In the subgroup analyses based on average adherence, the risk of virological detection was similar between all ARVs among PLWH with >95% adherence levels (Table 3) in multivariate analysis. Among PLWH with ≤95% adherence levels (Table 3) and compared to those receiving dolutegravir-based regimen, the risk of virological detection was significantly and independently increased for raltegravir-based regimen, NNRTIs and bPIs in multivariate analysis.

## **DISCUSSION**

In this cohort of PLWH followed by EDM, the adherence pattern to dolutegravir-based triple therapy was not a predictor of suppressed HIV-RNA. This picture contrasts with the strong association between adherence pattern and HIV-RNA level found for older regimens, including raltegravir, NNRTI and bPI-based ARV therapies. In addition, the use of dolutegravir therapy outperformed all other ARV strategies in term of virological suppression below the limit of detection among PLWH in the lower adherence subgroup, in multivariate analysis adjusting for age, sex, CD4 cell count and group (starting, switching and failing) and baseline HIV-RNA. No emerging mutation conferring resistance to INSTI was detected in the dolutegravir group with detectable HIV RNA, in contrast with the raltegravir group. Taken together, these results suggest that dolutegravir-based ARV therapies are more forgiving to missed doses (either by average adherence or treatment interruptions) than the other investigated ARV regarding the risk of HIV-RNA replication. In addition, dolutegravir-based triple therapy is more forgiving to missed doses than raltegravir-based triple therapy regarding the risk resistance.

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Most of the previous studies in this area of research attempted to identify an adherence threshold required for virological suppression with the aim to challenge the >95% historical threshold. For example, Byrd et al[8] reported that 75% average adherence defined by pharmacy refill to INSTI-based ARV therapy was required to suppress 90% of the treated patients. In this large cohort, first- and second-generations INSTI were pooled although we found the level of forgiveness between dolutegravir and raltegravir strongly differed (as suggested in Figure 2A and 2B, respectively). Overall, the multivariate analysis of the risk of virological replication (Table 1, n=399) is consistent with the >80% level of average adherence found in other studies[2,7,8] but reaffirms the importance of treatment interruption length (aOR, 4.6; 95% CI [1.3 - 16.9], p=0.02), as an independent risk factor[9,10,16].

Importantly, the use of dolutegravir was significantly and independently associated with a lower risk of virological replication compared to other ARVs in the subgroup with lower adherence. Although the 95% confidence intervals were large due to smaller sample size in this subgroup, this superiority is consistent with a network meta-analysis of 20 randomized trials in which a significantly higher proportion of naïve PLWH starting dolutegravir achieved virological suppression at week 96 compared to protease inhibitors, efavirenz and cobicistat-boosted elvitegravir[17]. The pharmacokinetic forgiveness of dolutegravir-based regimen is supported by the 14 hours dolutegravir terminal elimination half-life and its duration of inhibitory effect (>2-fold higher than the IC90 for 72 h after the last dose)[18]. In contrast, raltegravir, boosted atazanavir and boosted lopinavir have shorter terminal elimination half-life, respectively 10-12[19], 8.3 and 2.4 hours[20]. NNRTIs do have a long plasma half-life but a relatively low genetic barrier to HIV-1 resistance. While a prolonged plasma exposure improves pharmacokinetic forgiveness[21], a period of functional

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monotherapy following NNRTI-based treatment interruption may select for low-frequency resistant strains. Despite a high genetic barrier, dolutegravir monotherapy does promote INSTI-resistant strains[22] but only after a long period of exposure. This scenario is unlikely to occur when combined with other nucleosides in a fixed dose combination or when combined with nucleotides dosed once-daily whose anabolites have long intracellular half-lives.

There are several important limitations to this study. Adherence was monitored by EDM so we cannot prove that the ARVs were ingested. The duration of the study, 6 month was short and any virologic breakthrough before 6 month remained unnoticed. We compared non-randomized groups of PLWH with different baseline characteristics. In particular, the distribution of PLWH who started treatment as a switch, treatment failure and first therapy was different among treatment groups (Table 1). The use of multivariate analysis adjusting for important predictors of virological replication may have contributed to attenuate this risk of bias, although residual confounding may remain. The cohorts comparing different treatment groups were not contemporaneously studied. We investigated dolutegravir-based triple therapy. Therefore, our results regarding dolutegravir should not be generalized to dual-therapies (with either rilpivirine or lamivudine) or to bictegravir-based triple therapy. Further reseach in this area is warranted.

The study has also strengths. Our large sample size of 399 PLWH representing 73,017 EDM events with various ARV including dolutegravir makes this cohort unique. The diversity of ARV and adherence pattern behaviors allowed us to identify significant interactions between average adherence and treatment interruption. While prior work have demonstrated that short-term treatment interruptions can be reliably predicted by average adherence[23], our results suggest that: (i) they are not interchangeable

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measures[24]; (ii) their influence differs by ARV[21]. In addition, the use of historical controls allowed contrasting virological outcomes with dolutegravir to older regimens at similar adherence patterns (Figure 2A to D) or different adherence strata (Table 3).

Consistently high adherence should remain the goal of treatment, despite the high rates of suppression across a wide range of adherence level and patterns suggest a high degree of short-term forgiveness on dolutegravir-based regimens. Low levels of tenofovir by dried blood spots predicted future virological replication among PLWH receiving INSTI-based regimens (adjusted Odds Ratio, 1.9, 95% confidence interval [1.0 – 3.4],  $p=0.036$ )[25]. Moreover, suboptimal adherence[26] to ARVs and ARVs treatment interruptions[27] were both associated with higher levels of inflammation amongst people with full suppression and is associated with clinically significant morbidity in treated PLWH.[28]

As the WHO recommends, the transition from NNRTIs- to dolutegravir-based HIV treatment regimens in resource-limited settings should limit the risk of resistance following unstructured drug interruption due to toxicities, poor retention in care and drugs being out of stock locally. Our results are in line with the current International Antiviral Society-USA Panel guideline[29] in which second-generation INSTIs are preferred ARV treatment for most PLWH. However, our results do not support the European AIDS Clinical Society 2020 guideline[30]. Starting a raltegravir-based regimen as preferred initial antiretroviral therapy may expose PLWH with suboptimal adherence to the risks of incomplete viral replication and potential emergence of resistance to INSTI.

In conclusion, our findings suggest that PLWH treated with dolutegravir-based combination may be at lower risk of detectable virological replication than those treated

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with older regimens at similar low-to-moderate adherence levels. While many factors not evaluated in this work should influence the choice of ARV therapy, including tolerance, pill burden, PLWH preference, the risk of drug-drug interaction and costs, we recommend using dolutegravir-based regimens for PLWH who struggle to achieve high levels of adherence or at risk of treatment interruptions.

#### **FUNDING**

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#### **AVAILABILITY OF DATA AND MATERIALS**

A full dataset is available on reasonable request to the corresponding author.

#### **CONTRIBUTORS**

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JJP, LC, MC, DRB and LH designed the study. The DOLUTECAPS investigators enrolled patients in the study and were involved in acquisition of data, and JJP, LC, MPS, ME, GU, PP, AGB, TP, MC, RV and LH collected data. JJP, ALF, JJD, EML and FC analysed data. JJP, MC and LH contributed to protocol concept and design and clinical oversight of the study. JJP provided statistical expertise. JJP, ALF, LC, MPS, DRB, MC, RV and LH participated in data interpretation and drafted the report. All authors have provided input to the report and approved the final version.

#### **TRANSPARENCY DECLARATIONS**

Dr. Parienti reports personal fees and non-financial support from Gilead Sciences, MSD, and ViiV Healthcare, outside the submitted work. Dr. Cotte reports personal fees and non-financial support from Abbvie, Janssen Cilag, Gilead Sciences, MSD, and ViiV Healthcare, outside the submitted work. Dr. Hocqueloux has received personal fees from Abbvie, Gilead, Janssen, Merck, and ViiV Healthcare, outside the submitted work. All other authors report no potential conflicts.

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Table 1. Baseline and follow-up characteristics by antiretroviral class

Variables	Dolutegravir-based (n=102)	Raltegravir-based (n=90)	NNRTI-based (n=100)	bPI-based (n=107)	p-value
Baseline characteristics					
Age, mean (SD), years	47.7 (13.2)	46.2 (11.2)	46.8 (10.6)	41.3 (7.6)	<0.001
Male, sex, n(%)	73 (72)	65 (72)	86 (86)	88 (82)	0.028
CD4+ cells, median (IQR)	494 (290 - 705)	490 (309 - 709)	510 (383 - 723)	311 (229 - 450)	<0.001
Treatment groups, n (%) / Log HIV-1 RNA, median [IQR]					
Switched treatment	47 (46) / 1.7	69 (77) / 1.7	100 (100) / 1.7	31 (29) / 1.7	
Treatment-naïve	26 (26) / 4.6 [4.0-5.0]	10 (11) / 5.4 [3.6-5.5]	0 (0) / -	43 (40) / 4.4 [3.8-5.1]	<0.001
Failed treatment	29 (28) / 3.2 [2.6-4.1]	11 (12) / 4.6 [4.0-5.0]	0 (0) / -	33 (31) / 2.8 [2.3-3.6]	
Backbone					
TDF/FTC or TAF/FTC	22 (22)	49 (54)	22 (22)	56 (52)	
ABC/3TC	47 (46)	6 (7)	38 (38)	10 (9)	
Other NRTIs combination	8 (8)	12 (13)	40 (40)	13 (12)	
Other class combination	25 (25)	23 (26)	0 (0)	28 (26)	<0.001
Adherence follow-up					
Average adherence, median (IQR)	96.0 (87.0 - 99.0)	97.0 (91.0 - 100.0)	96.0 (84.5 - 99.0)	95.3 (82.0 - 100.0)	0.32
Longest TI in days, median (IQR)	2.1 (1.3 - 2.8)	1.5 (1.0 - 2.7)	1.3 (1.1 - 1.9)	2.0 (1.0 - 7.0)	<0.001

Abbreviations: bPI, boosted protease inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor ; TDF, tenofovir ; FTC, emtricitabine ;TAF, tenofovir alafenamine ; ABC, abacavir ; 3TC, lamivudine ; NRTI, Nucleoside Reverse Transcriptase Inhibitor ; TI, treatment interruption

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Table 2. Factors associated with virological replication (>50 copies/mL) at month-6 in the overall cohort (n=399)

Variables	Univariate analysis			Multivariate analysis	
	No VR (n=335)	VR (n=64)	p-value	aOR [95%CI]	p-value
Age, mean (SD)	44.5 (11.8)	41.6 (11.3)	0.07	0.88 [0.63 - 1.22]	0.44
Male	259 (77.3)	53 (82.8)	0.41	1.36 [0.6 - 3.2]	0.48
CD4 cells, mean (SD)	494 (256)	402 (250)	0.009	0.97 [0.86 - 1.14]	0.92
Log HIV-RNA, cp/mL, mean (SD)	2.44 (1.23)	2.90 (1.37)	0.008	1.61 [0.97 - 2.68]	0.07
Third antiretroviral agent			0.005		
Dolutegravir-based	94 (28.1)	8 (12.5)		Ref.	
Raltegravir-based	72 (21.5)	18 (28.1)		7.7 [2.4 - 25.2]	0.0007
bPI-based	81 (24.2)	26 (40.6)		1.9 [0.6 - 6.0]	0.29
NNRTI-based	88 (26.3)	12 (18.8)		3.4 [0.9 - 12.7]	0.07
Treatment Group			<0.0001		
Switched treatment	221 (66.0)	26 (40.6)		Ref.	
Treatment-naïve	70 (20.9)	9 (14.1)		0.6 [0.1 - 4.2]	0.63
Failed treatment	44 (13.1)	29 (41.3)		4.4 [1.4 - 14.0]	0.012
Adherence class			<0.0001		
>95%	211 (63.0)	20 (31.2)		Ref.	
[90%-95%[	39 (11.6)	3 (4.7)		0.5 [0.1 - 2.1]	0.35
[80%-90%[	47 (14.0)	5 (7.8)		0.8 [0.2 - 2.6]	0.69
[60%-80%[	29 (8.7)	13 (20.3)		3.2 [1.0 - 10.0]	0.043
<60%	9 (2.7)	23 (35.9)		5.9 [1.5 - 23.7]	0.012
Longest treatment interruption in hours, Log mean (SD)	1.63 (0.28)	2.06 (0.48)	<0.0001	4.6 [1.3 - 16.9]	0.02

Abbreviations: VR, virological replication with HIV-RNA>50 cp/mL; aOR, adjusted odds ratio; CI, confidence interval; bPI, boosted protease inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor



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Table 3. Predictors of virological replication by average adherence subgroups in multivariate analysis\*.

Third antiretroviral agent	Higher adherence (>95%) n=211		Lower adherence (≤95%) n=188	
	aOR [95%CI]	p-value	aOR [95%CI]	p-value
Dolutegravir-based	Ref.		Ref.	
Raltegravir-based	3.7 [0.9 - 16.1]	0.08	45.6 [4.5 - 462.1]	0.001
bPI-based	0.6 [0.1 - 3.1]	0.50	28.3 [3.4 - 239.4]	0.002
NNRTI-based	3.4 [0.3 - 36.2]	0.31	24.8 [2.7 - 228.4]	0.005

\*Adjusting for age, sex, baseline CD4 cells, baseline HIV-RNA, treatment group (failing, switching or starting) Abbreviation: NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor, bPI, Boosted Protease Inhibitor;

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Figure 1. Virological replication levels (Log HIV-RNA) at 6-month by electronic drug monitoring (EDM) adherence pattern according to antiretroviral regimen class (n=399). Each circle symbol represents a people living with HIV (PLWH) connected to the plane by a vertical needle. The length of the needle represents the HIV-RNA level of replication at 6 month in log cp/mL (Z-axis). The horizontal plane coordinates correspond to the EDM defined adherence pattern during the 6 months period with the average adherence on the X-axis and the longest treatment interruption in log<sub>10</sub> hours on the Y-axis. PLWH with higher adherence are those on the bottom corner.

Abbreviation: DTG, Dolutegravir; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor, NVP, nevirapine; EFV, Efavirenz; RPV, Rilpivirine; bPI, Boosted Protease Inhibitor; LPV/r, Lopinavir/Ritonavir; ATV/r, Atazanavir/Ritonavir

Figure 2. Surface forgiveness plot and linear regression models of adherence patterns explaining HIV-RNA by antiretroviral regimen.

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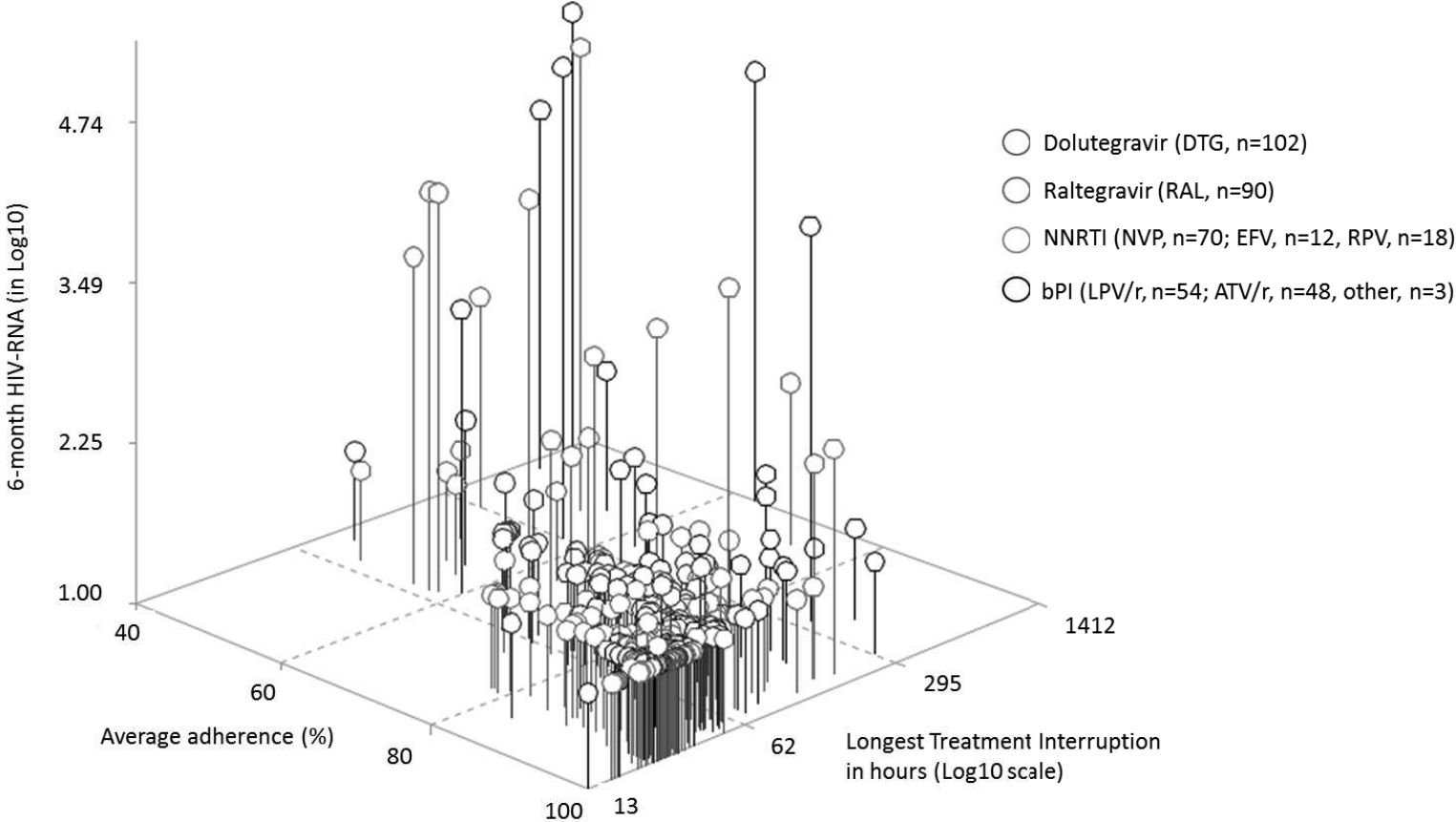
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Figure 1.



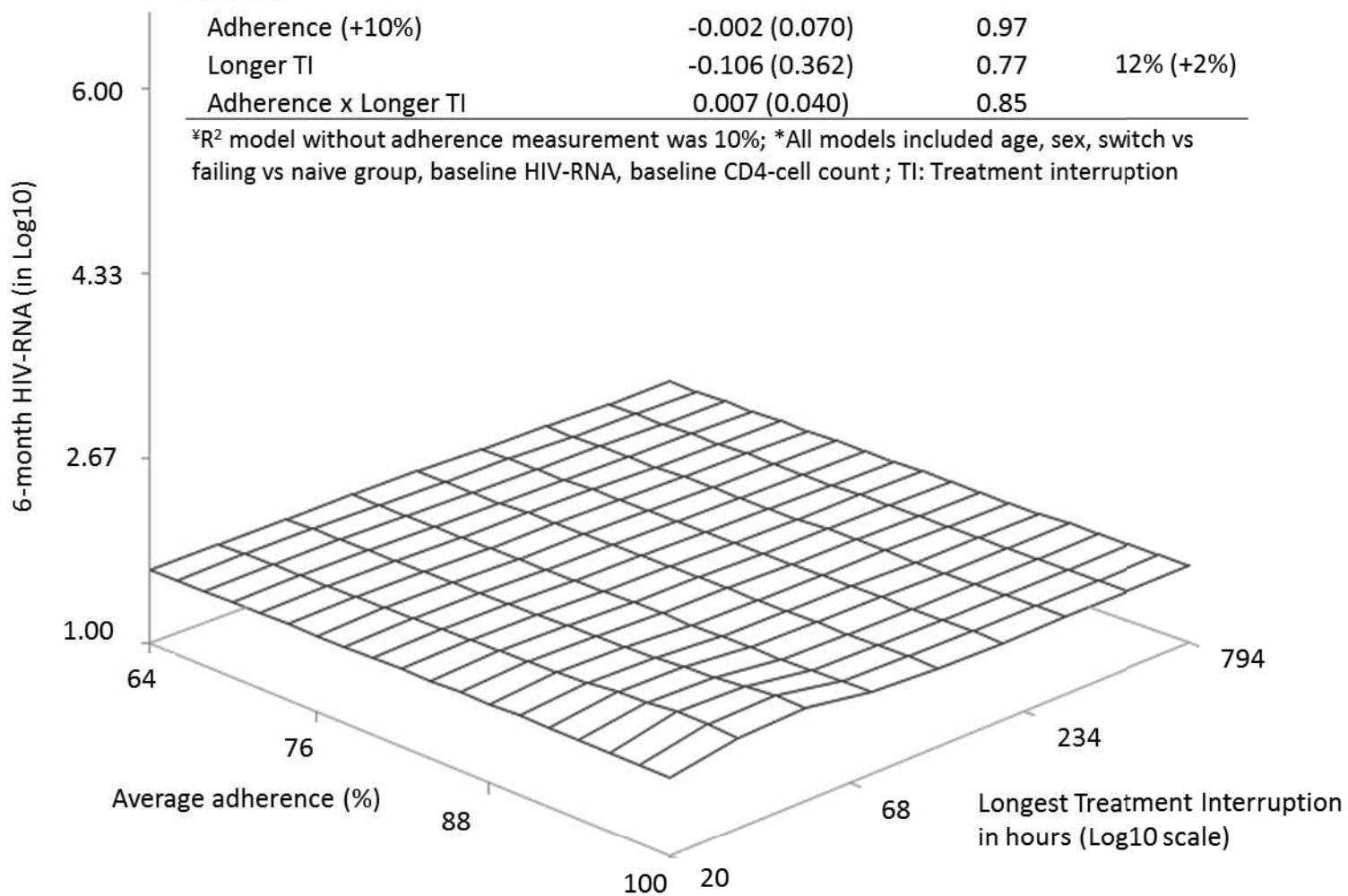
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Figure 2A.

Dolutegravir-based (n=102)

	$\beta$ (SE)	P-value	R <sup>2</sup> ‡
<i>Model 1*</i>			
Adherence (+10%)	0.017 (0.010)	0.12	12% (+2%)
<i>Model 2*</i>			
Longer TI	0.076 (0.049)	0.13	12% (+2%)
<i>Model 3*</i>			
Adherence (+10%)	-0.002 (0.070)	0.97	
Longer TI	-0.106 (0.362)	0.77	12% (+2%)
Adherence x Longer TI	0.007 (0.040)	0.85	

‡R<sup>2</sup> model without adherence measurement was 10%; \*All models included age, sex, switch vs failing vs naive group, baseline HIV-RNA, baseline CD4-cell count ; TI: Treatment interruption



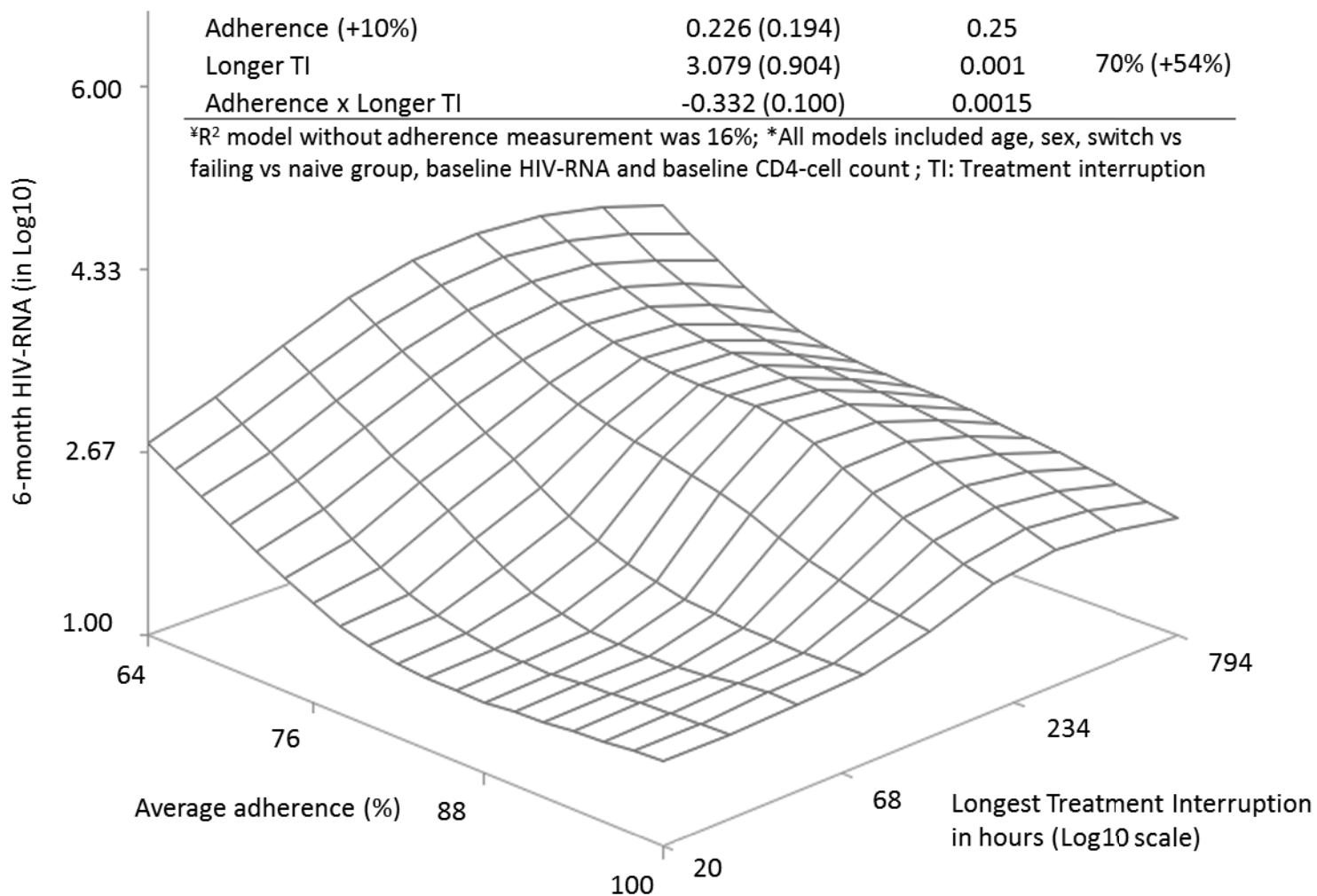
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Figure 2B.

Raltegravir-based (n=90)

	$\beta$ (SE)	P-value	R <sup>2</sup> ‡
<b>Model 1*</b>			
Adherence (+10%)	-0.420 (0.039)	<0.001	65% (+49%)
<b>Model 2*</b>			
Longer TI	0.954 (0.182)	<0.001	37% (+21%)
<b>Model 3*</b>			
Adherence (+10%)	0.226 (0.194)	0.25	
Longer TI	3.079 (0.904)	0.001	70% (+54%)
Adherence x Longer TI	-0.332 (0.100)	0.0015	

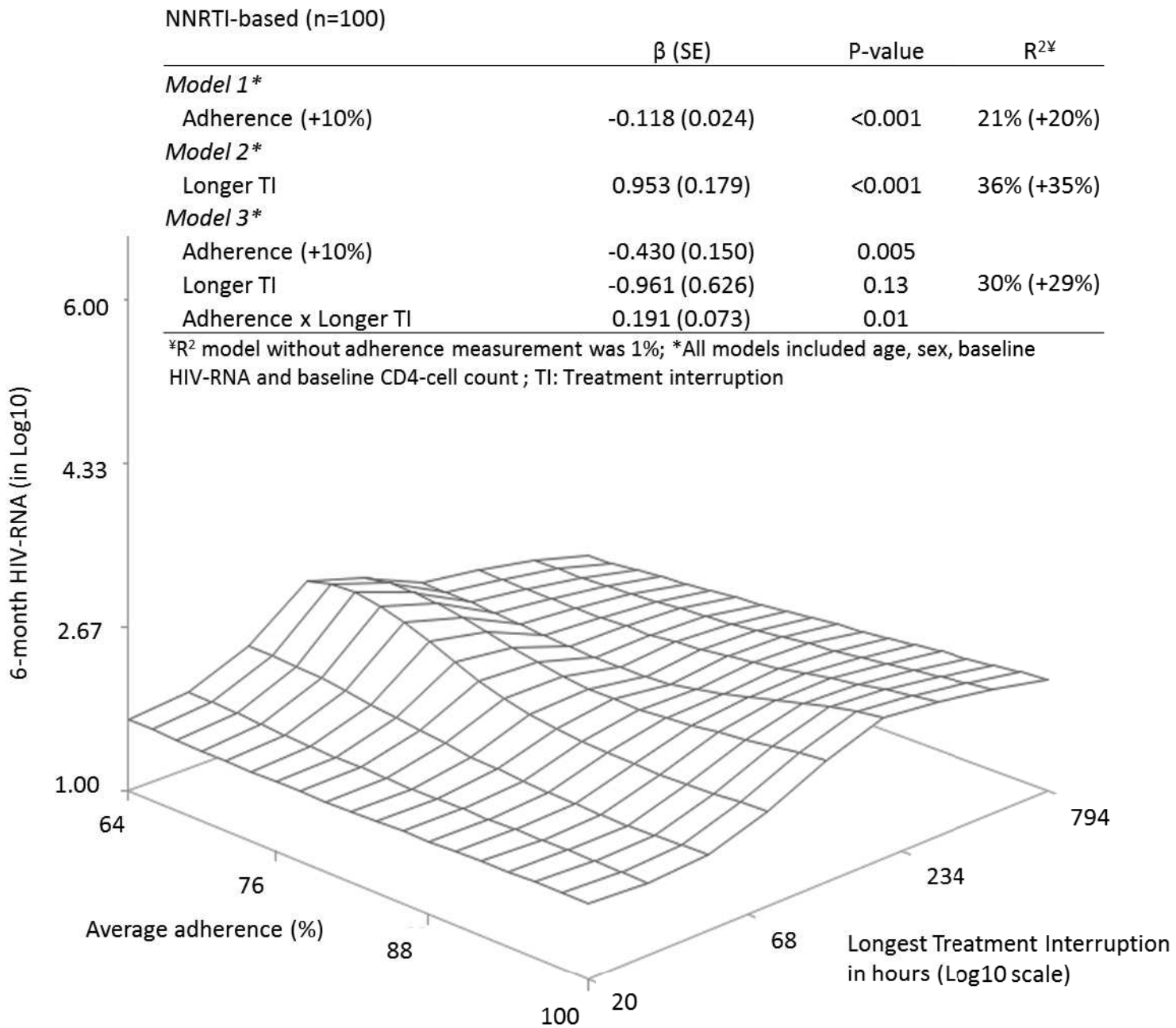
‡R<sup>2</sup> model without adherence measurement was 16%; \*All models included age, sex, switch vs failing vs naive group, baseline HIV-RNA and baseline CD4-cell count ; TI: Treatment interruption





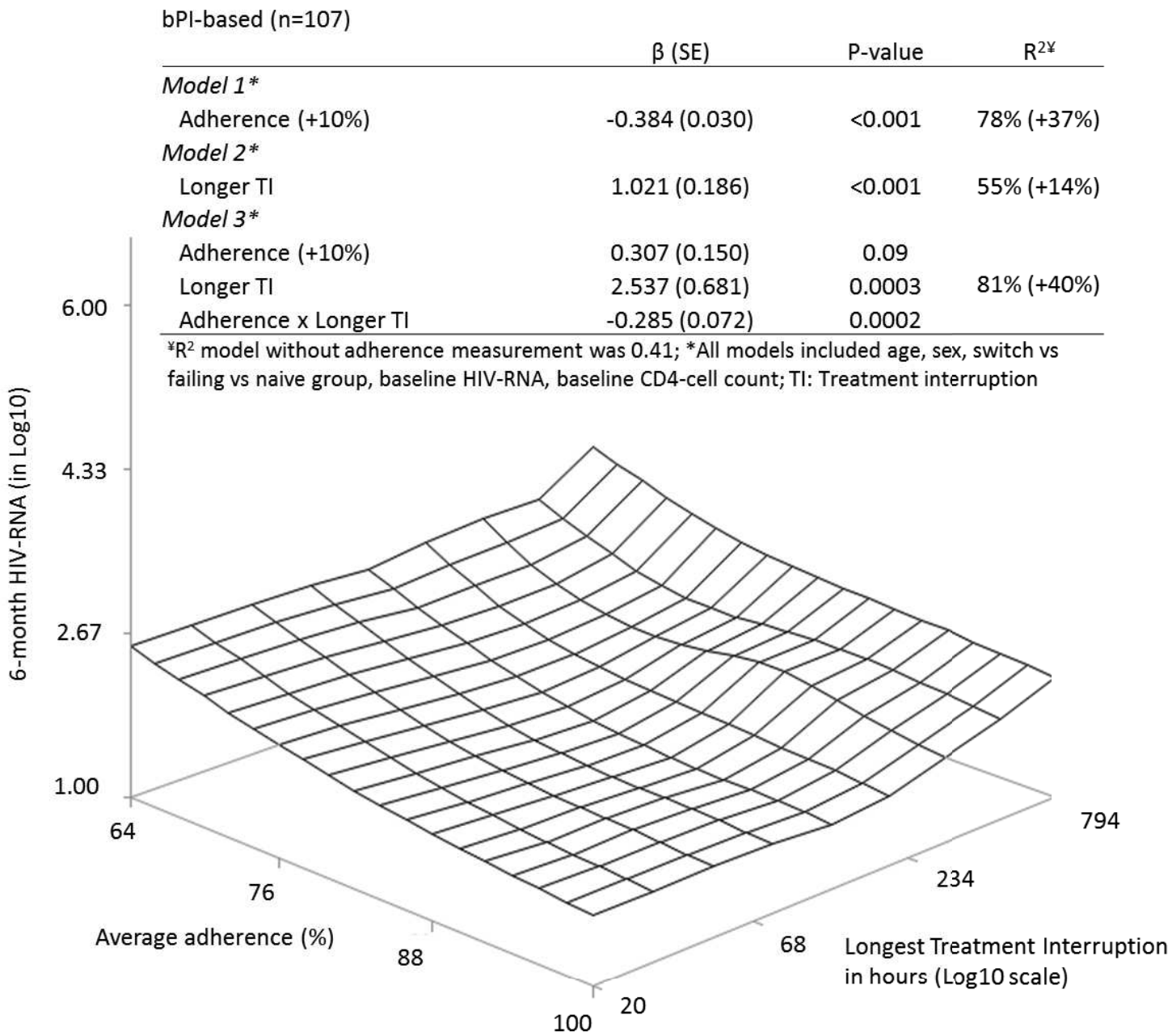
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Figure 2C.



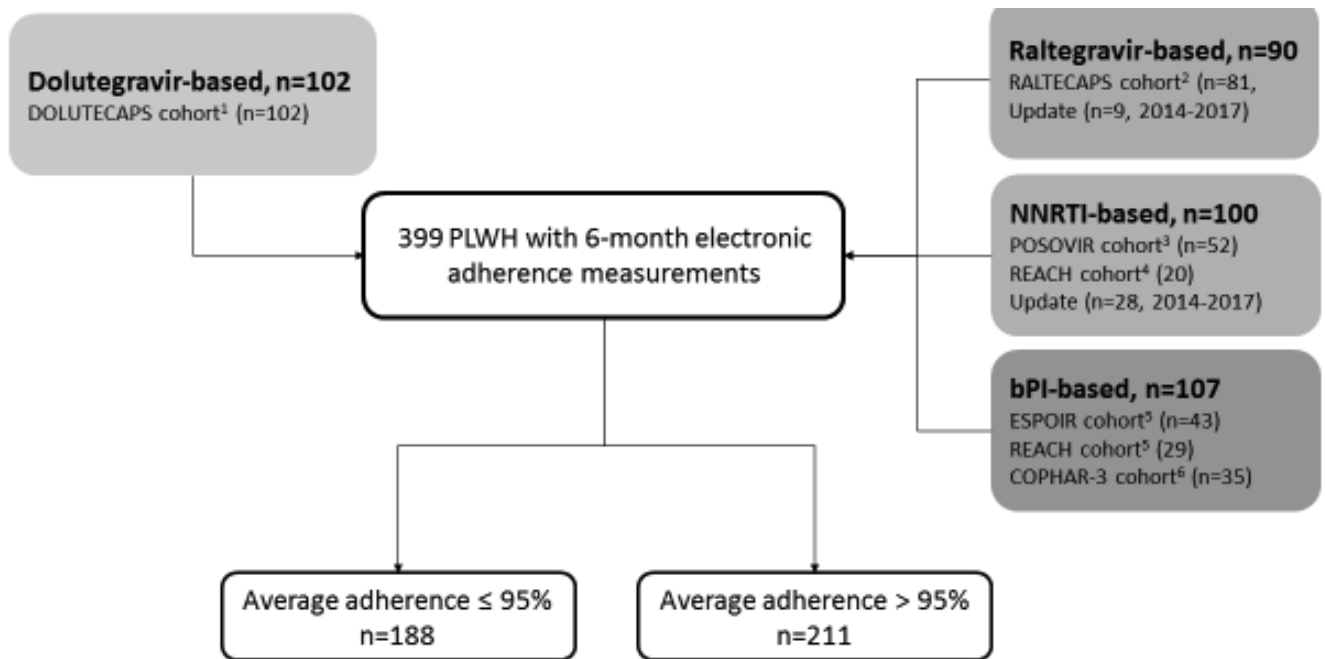
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Figure 2D.



**SUPPLEMENTAL APPENDIX**

Figure S1.



<sup>1</sup>Clinicaltrial.gov NCT02878642; <sup>2</sup>Gras *JAIDS* 2012; <sup>3</sup>Parienti *AIDS* 2007; <sup>4</sup>Parienti *PLoS ONE* 2008; <sup>5</sup>Parienti *Clin Infect Dis* 2010; <sup>6</sup>Parienti *AAC* 2013

## **IV. Étude des facteurs associés à l'échec virologique sous dolutégravir en monothérapie**

### **a) Résumé**

Nous avons souhaité déterminer les facteurs associés à l'échec virologique sous DTG-m en traitement de maintenance, puis explorer l'hétérogénéité du risque d'échec comparé à une trithérapie classique, en fonction des FDR identifiés. En objectifs secondaires, nous avons étudié les effets secondaires sous DTG et l'émergence de résistance aux INI en cas d'échec virologique.

Nous avons réalisé une méta-analyse sur données individuelles des essais cliniques réalisés jusqu'à maintenant ayant évalué le DTG-m. La population d'étude était constituée de PVVIH contrôlées sur le plan virologique depuis plus de 6 mois, et suivies pendant 48 semaines. L'échec virologique était défini par deux CV > 50 copies/mL avant la semaine 48. Un modèle de Cox a permis de déterminer les FDR d'échec sous DTG-m à partir de la base de données de tous les individus ayant reçu le DTG-m. Puis, nous avons exploré l'hétérogénéité du risque d'échec virologique sous DTG-m comparé à la trithérapie standard, par une analyse en sous-groupes en fonction des FDR.

Quatre essais cliniques randomisés ont été inclus soit 416 PVVIH, 101 de l'essai suisse EARLY-SIMPLIFIED, 95 de l'essai hollandais DOMONO, 62 de l'essai espagnol DOLAM et 158 de l'essai français MONCAY. Seize échecs furent retrouvés, tous dans le groupe expérimental. Parmi 272 PVVIH traitées par DTG-m, les facteurs indépendants d'échec virologique étaient le nadir de CD4 < 350 cellules/mm<sup>3</sup> ; un délai entre le diagnostic du VIH et le premier ARV > 90 jours ; un taux d'ADN proviral à l'inclusion  $\geq 2,7 \log/10^6$  PBMCs et la présence d'un signal PCR d'ARN VIH plasmatique à l'inclusion. Nous avons trouvé que l'échec virologique était expliqué en majeure partie par le niveau d'ADN proviral à l'inclusion ( $I^2=80,2\%$ ). Une différence de risque de 32% entre le groupe DTG-m et le groupe contrôle, existait parmi les PVVIH avec un taux d'ADN proviral  $\geq 2,7 \log/10^6$  PBMCs.

Ces résultats éclairent le clinicien sur le risque encouru sous monothérapie de DTG en fonction des caractéristiques individuelles du patient, en particulier le taux d'ADN proviral à l'inclusion.

**b) Publication n°4**

**Dolutegravir monotherapy as maintenance strategy: an individual-participant meta-analysis of randomized controlled trials**

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## ABSTRACT

**Background :** In order to improve tolerance to antiretroviral therapy (ART) and also to reduce healthcare costs, several maintenance strategies have been studied. We sought to identify the risk factors of virological failure (VF) under DTG in monotherapy (DTG-m) and to explore the heterogeneity of the risk as compared to a combined ART (cART), according to the identified risk factors.

**Methods :** We searched PubMed, Embase, the Cochrane database, and conference abstracts for randomized clinical trials (RCT) evaluating DTG-m versus cART. Eligible studies included trials of HIV-positive adults virologically controlled for at least 6 months, and followed for 48 weeks. Definition of VF was a confirmed viral load > 50 copies/ml before W48. We performed a single stage individual participant data meta-analysis of the DTG-m VF risk factor and a two-stage analysis of the risk difference of VF between DTG-m and cART. The study was registered with PROSPERO (number CRD42020221501).

**Findings :** We included 416 PLWH from four European RCTs. Sixteen failures occurred, all in the experimental group DTG-m. Among 272 participants under DTG-m, VF were more likely in participants who initiated first ART  $\geq 90$  days from HIV diagnosis (hazard ratio [HR] 5.16; 95% confidence interval (95% CI) 1.72-15.49), had a nadir of CD4 T cells < 350/mm<sup>3</sup> (HR 12.10; 95% CI 2.31-63.33), a detected plasma HIV RNA signal at baseline (HR 4.84; 95% CI 1.67-14.03) and an HIV DNA level at baseline  $\geq 2.7/10^6$  PBMCs (HR 3.81; 95% CI 1.28-11.37). The highest risk difference between DTG-m and cART group was found when HIV DNA level was  $\geq 2.7 / 10^6$  PBMCs (32%). The VF risk difference could be explained by HIV DNA level ( $I^2=80.2\%$ ).

#### IV. Facteurs associés à l'échec virologique sous dolutegravir en monothérapie

**Interpretation :** Our study highlights the importance to explore the level of proviral DNA in simplification strategies decreasing the burden of antiretroviral therapy such as DTG-m. We have identified several factors associated with VF that could help to re-define in the future the potential role of DTG-m in selected patients.

**Funding :** The study was not funded.

**Keywords :** dolutegravir, monotherapy, hospital cohort, HIV, individual-participant data meta-analysis

### RESEARCH IN CONTEXT

#### **Evidence before this study**

We searched Medline, EMBASE, Cochrane Central and Web of Science, using the keywords 'dolutegravir (DTG) monotherapy' and 'virological failure' up through April 21<sup>st</sup>, 2021. Twenty-three single studies were identified, four of which were reviews, and four RCTs published between 2017 and 2019. One meta-analysis synthesized a rate of virological failure with DTG-m at week-48 of 8.9% (95% confidence interval 4.7-16.2) in a descriptive aggregate-data meta-analysis involving two randomised controlled trials (DOMONO(1) and DOLAM) and 6 observational studies. Since then two others randomized controlled trials were developed (EARLY-SIMPLIFIED and MONCAY). In DOMONO, DOLAM and MONCAY study, DTG-m was found non inferior to cART at W24 but virological failure and integrase strand transfer inhibitor (INSTI) resistance were found thereafter. EARLY-SIMPLIFIED found a non-inferiority of DTG-m versus cART at 48 weeks among primary HIV infection. The group of investigators who performed the DOMONO trial did investigate virological failure risk factors under DTG-m, but their analysis was hampered by the small sample size.

#### IV. Facteurs associés à l'échec virologique sous dolutegravir en monothérapie

Among 78 participants, a low CD4 T-cell nadir, a long time between HIV diagnosis and combined antiretroviral therapy (cART) initiation and a high HIV DNA level were found to be associated with virological failure in univariate analysis.

#### ***Added value of this study***

Our study uses individual participant data from the four randomized controlled trials of DTG-m versus cART to examine the impact on virological outcome according to individual characteristics, such as sex, age, history of HIV infection, CD4 T-cell count, a HIV RNA PCR signal or a HIV DNA level. Additionally, we evaluate the emergence of integrase inhibitor resistance and the safety of DTG.

We publish the first multivariate model of virological failure risk factors under DTG-m. Participants under DTG-m had an increasing risk of virological failure if the time before first ART was  $\geq 90$  days from the HIV diagnosis date, the nadir of CD4 T cells was  $< 350/\text{mm}^3$ , when a plasma HIV RNA signal was detected at baseline and when the HIV DNA level at baseline was  $\geq 2.7/10^6$  PBMCs. The highest risk difference between DTG-m and cART was found when HIV DNA level was  $\geq 2.7 / 10^6$  PBMCs (32%) and moreover, the highest heterogeneity was found in the HIV DNA level subgroup analysis. Indeed, 80.2% of the virological failure risk difference between DTG-m and cART could be explained by HIV DNA level.

#### ***Implications of all the available evidence***

Our study highlights the importance to explore the level of proviral DNA in simplification strategies decreasing the burden of antiretroviral therapy such as DTG-



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m. We have identified several factors associated with VF that could help to re-define in the future the potential role of DTG-m in selected patients.

## INTRODUCTION

Current recommended potent antiretroviral combinations include triple- or dual-integrase strand transfer inhibitor (INSTI) based regimen. (2–4) The large majority of PLWH are virologically controlled and then non-transmitters without AIDS related complications. However, the antiretroviral treatment of HIV infection requires a life-long therapy, which is associated with side-effects, pill burden, drug-drug interactions and long-term complications particularly for ageing PLWH. (5,6) In an effort to improve quality of life, tolerance and decrease healthcare-related costs, several maintenance strategies have been investigated. (7–17)

Dolutegravir is a once-daily second generation INSTI with high potency, high genetic barrier to resistance, high forgiveness to missed doses, good safety profile and few drug-drug interactions. (1,18–22) These characteristics placed dolutegravir monotherapy (DTG-m) as a good candidate for maintenance therapy. Unfortunately, most studies evaluating DTG-m provided disappointing results. For example, Calmy et al. synthesized a rate of virological failure with DTG-m at week-48 of 8.9% (95% confidence interval (95% CI) 4.7-16.2) in a descriptive aggregate-data meta-analysis involving two randomised controlled trials (DOMONO (1), DOLAM (23)) and 6 observational studies. (24) In addition, resistance mutations developed in seven (3.6%) participants on DTG-m. Since then, two additional randomised controlled trials evaluating DTG-m maintenance have been published, namely MONCAY and EARLY-SIMPLIFIED trials. (25,26) Although the DTG-m had an unacceptable rate of

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failure, many of the participants receiving DTG-m were able to control HIV-RNA replications. The knowledge of independent factors associated with DTG-m virological failure are of interest in the era of bitherapy including an INSTI plus a second drug with low genetic barrier to resistance and then at risk of functional monotherapy. (2,14–17,27) However it requires individual-level participants data and large sample size to perform multivariate analysis. The group of investigators who performed the DOMONO trial did investigate this research question, but their analysis was hampered by the small sample size. (1,28) Among 78 participants, a low CD4 T-cell nadir, a long time between HIV diagnosis and combined antiretroviral therapy (cART) initiation and a high total peripheral blood mononuclear cell (PBMC) HIV DNA copy number were found to be associated with virological failure in univariate analysis.

We first aimed to explore the influence of participant-level covariates on the risk of DTG-m virological failure using all available evidence from randomised controlled trials. Based on the variables identified to be independently associated with DTG-m virological failure, we secondly explored the heterogeneity of the risk of DTG-m failure as compared with cART through an individual participant data meta-analysis (IPDMA).

## **METHODS**

### ***Study oversight and search strategy***

We conducted an IPDMA according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines for the meta-analysis of randomized controlled trials. (29) Our protocol was prospectively registered in

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PROSPERO (number CRD42020221501). We searched Medline, EMBASE, Cochrane Central and Web of Science, using the keywords 'dolutegravir monotherapy' and 'virological failure'. Furthermore, we searched clinicaltrials.gov for unpublished studies. The last search was conducted on April, 21st, 2021. We considered all RCTs investigating DTG-m. Participant characteristics of eligible studies included aged 18 or above, virologically controlled HIV-1 infected participants (plasma HIV RNA <50 copies/ml) for at least 6 months at the time of screening, and randomly assigned them to receive DTG-m or cART. No language restrictions were applied. Studies had to report on virological outcomes of participants who switched to a DTG monotherapy after having an undetectable VL on cART. Two investigators (AF and JJP) independently selected studies based on titles and, in a second step, assessed the eligibility based on the full articles text. Corresponding authors of eligible studies were asked to participate to a European Collaborative group to perform an IPDMA by sharing their original study database.

The Caen University Hospital signed a data sharing agreement with all corresponding author institutions. All the participants provided written informed consent to participate to the RCTs and agreed for further research based on the anonymized data collected along the RCTs. All the parent studies received approval from independent ethics committee, as appropriate.

#### ***Data collection and management***

The following data were extracted independently at the study-level by two reviewers (AF and JJP), using a standardized spreadsheet: inclusion and exclusion criteria, definitions of outcomes, number of participants and their main demographic and clinical characteristics, including immunological status (CD4 cell count at baseline and

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nadir), virological parameters (HIV-RNA at baseline, HIV-DNA at baseline and at week 24 and 48) and HIV integrase mutations.

Regarding individual-level variables, the data manager of each qualified study performed a de-identified individual data extraction including the prespecified following variables : trial arm, date of inclusion, sex, age at inclusion, ethnicity, HIV transmission risk, nadir CD4 T-cell count, date of HIV diagnosis, prior exposure to INSTI, previous genotypic resistance to any ART, previous genotypic resistance to any INSTI, presence of a PCR signal below the quantification threshold, CD4 T-cell count, HIV-1 DNA, at baseline and at week 24, virologic failure and HIV integrase mutations. A binary variable HIV DNA count at baseline was created with a cut-off at  $2.7 / 10^6$  PBMCs according to Trulight study. (7) We built a binary variable nadir of CD4 T cells count with a cut-off of 350 cells/mm<sup>3</sup> and a time before first ART with a cut-off at 90 days according to the medians. After validation by each DM of the parent studies, we merged participants into one database formatted with a common naming structure.

For quality control, we compared data collected from the original papers and from the database shared by authors. In cases of discrepancies from the published article or trial protocol, the authors were contacted for clarification. The methodological components of the randomised trials such as blinding (participants, personnel and outcome assessor), incomplete outcome data, and other sources of bias were assessed by two independent authors (ALF and JJP) as recommended by the Cochrane collaboration. (30)

#### **Outcomes**

The primary end-point was virological failure, defined as two consecutive viral loads >50 copies/mL during follow-up. Our main outcome was to determine overall risk

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difference of virological failure between DTG-m arm and cART arm. The secondary outcomes of the study were the safety and the emergent genotypic resistance to the INSTI class in case of virological failure. Definition of virological failure was a confirmed VL > 50 copies/ml before W48. Only DOMONO trial has used a different definition of virological failure, VL >200 copies/ml, but their investigators could update the outcome variable to fit with the new definition (Supplemental Figure S1).

#### **Statistical analysis**

No sample size was estimated *a priori* and all available data were used. Analyses were conducted on the intention to treat dataset for three studies and on treatment dataset for one study. The statistical analysis plan had two objectives: (i) identify risk factors for DTG-m virological failure and (ii) explore heterogeneity of the effect size between subgroups stratified by previously identified risk factors.

Regarding risk factors, we analysed all patients who received DTG-m during the follow-up into a single-stage meta-analysis. (19) Continuous variables were presented as means with standard deviations or as medians with interquartile ranges (IQR), as appropriate. Dichotomous or categorical variables were presented as the number and percentage of the study-specific or total study population. We computed uni- and multivariate Cox models of independent virological failure risk factors. Proportional risk assumption was tested by Schoenfeld residuals and time by covariate interactions. When this assumption was not met, we used log-rank test instead. In order to take into account the intra-study correlation, we used robust variance estimates in the Cox model. Colinearity was explored among independent variables, thru correlations matrix and variance inflation factor. A log-rank test was performed when univariate cox model was not applicable (for example no event in one subgroup). Statistical analyses and

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data preparation were conducted in STATA version 14.1 (StataCorp, Texas, USA) and SAS v.9.4 (SAS institute, NC, Cary).

Regarding heterogeneity, we secondly used all participants from the two randomized arms (DTG-m and controls). We estimated the incidence of virological failure and then compared time to virological failure between DTG-m arm and cART arm with a Kaplan-Meier method. Because no virological failure occurred in the control group, the use of Cox model was not appropriate and the effect size of the DTG-m was estimated by the absolute risk difference and 95% confidence interval (CI) of the cumulative risk of virological failure between DTG-m and cART. In order to take into account the intra-study correlation, we performed a two-stage meta-analysis. Subgroup analyses were defined according to the independent risk factors found in the multivariate analysis. We then compared proportions of virological failure between DTG-m arm and cART arm in each subgroups and estimated the absolute risk difference and 95% CI of virological failure in a Mantel-Haenszel model assuming random effects. We quantified the heterogeneity of this effect size by the  $I^2$ , which corresponds to the percentage of differences not explained by chance. Statistical analyses and data preparation were conducted in Revman v5 software.

## RESULTS

### *Study selection*

Twenty-three single studies were identified in the literature search, of which four were RCTs and were included in the meta-analysis: EARLY-SIMPLIFIED, Switzerland (25), DOMONO, The Netherlands (1), DOLAM, Spain (23) and MONCAY, France (26)

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(Supplemental Figure S2). Corresponding author of these trials were approached and they all agreed to collaborate in the DTG-m IPDMA project. We built a European collaboration together and each shared their database and answered to our requests. Their original databases were matched in an IPDMA data set.

##### ***Baseline characteristics : study level***

All the four trials evaluated DTG-m compared to cART as a maintenance therapy. Four hundred and sixteen subjects were enrolled, 101 subjects from the Swiss trial, EARLY-SIMPLIFIED; 95 from the Dutch trial DOMONO; 62 from the Spanish trial DOLAM and 158 in the French trial MONCAY. A description of the main studies characteristics is provided in Supplemental Table S1.

Eligibility criteria were adults with a history of controlled HIV infection (VL<50 copies/ml) for at least 6 months for DOMONO and 12 for the three others, no virological failure before nor previous resistance to INSTI. Nadir of CD4 T cells was a criterion according to DOMONO, DOLAM (>200 cells/mm<sup>3</sup>) and MONCAY (>100 cells/mm<sup>3</sup>). EARLY-SIMPLIFIED trial included individuals with a primary HIV-1 infection diagnosis and cART start within 180 days after.

Studies assessed virological outcomes at 48 weeks, the median of follow-up was 48 weeks (IQR = 24-48). Mean age of participants included was 46 years (min-max, 19-83) and 15% were female. Majority were men who have sex with men (69%) and Caucasian (87%). Time before first cART median was 91 days (IQR, 30-759). The mean nadir CD4 cell count was 362 cells/mm<sup>3</sup> (91-1,230).

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Quality of these studies was studied according to PRISMA score (Supplemental Figure S3). The review of the studies yielded to a moderate risk of bias, one had a low level (EARLY-SIMPLIFIED).

All RCTs were open-label non-inferiority trials, of which one was a single center trial and three were multicenter trials. Computerized randomization was used by the four studies : a web based block randomisation method with stratification by HIV RNA zenith for DOMONO, stratification by center for MONCAY; and a web based sequence randomization stratifying by anchor drug (PI, NNRTI or integrase inhibitor) for DOLAM. There was no evidence of selective reporting in any of the studies. There were 203 (48.8%) missing baseline HIV DNA (no baseline HIV DNA data from DOLAM, 4/101 missing data from EARLY-SIMPLIFIED, 18/95 from DOMONO and 119/158 from MONCAY). There were 63 (15.1%) missing data of time between HIV diagnosis and ART initiation (no data from DOLAM and one missing data from EARLY-SIMPLIFIED). There was one missing data for PCR signal at baseline. However, there was no missing outcome data. Patient retention was 386/416 (92.8%).

#### ***Baseline characteristics : individual level***

Two hundred and twenty seven individuals composed the DTG-m arm and 189 the cART arm. Baseline characteristics for the maintenance treatment group and control group were comparable (Table 1). Mean age was 45 (min-max, 22-82) in the DTG-m arm and 47 (19-83) in the cART arm,  $p=0.19$ . Median of time before first ART was 72 days (IQR, 29-547) for DTG-m versus 132 days (33-863),  $p=0.11$ . Twenty seven individuals were exposed to first INI generation in the DTG-m arm (12%) versus 33 (18%) in the cART arm,  $p=0.11$ . Three individuals in the DTG-m arm and two in the cART arm were known to have a previous genotypic resistance to an INSTI.



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Presence of a PCR signal at baseline represented 38 individuals under DTG-m (17%) and 34 under cART (18%),  $p=0.72$ . Mean of CD4 T cells at baseline was 786 (280-2,489) in the first group and 767 (243-1,803) in the second,  $p=0.49$ . Nadir of CD4 T cells count was  $<350$  for 129 (57%) of individuals under DTG-m and 114 (60%) under cART,  $p=0.47$ . HIV DNA count at baseline was  $\geq 2.7 / 10^6$  PBMCs for 27/133 individuals (20%) under DTG-m and 10/80 (13%),  $p=0.15$ .

#### ***Risk factors of DTG-m failure***

We pooled together all the participants under DTG-m in the four RCTs, 227 participants of the DTG-m arms plus 45 participants in the DOMONO trial switched under DTG-m at week 24. Among those 272 participants, 18 virological failure occurs. Incidence of virological failure was 1.69/1000 persons-years (95% CI 1.07-2.69). Median of DTG-m was 48 weeks (IQR, 24-48).

People with virological failure were all male, mean age of 50 years (min-max, 27-68), Caucasian for 83% and men who have sex with men for 67%. Nadir of CD4 T cells was  $< 350$  cells/mm<sup>3</sup> among 15/18 individuals with virological failure (83%). Median time between HIV diagnosis and first ART was 2.3 years (IQR, 0.6-4.2). Time before first ART was  $\geq 90$  days among 12/15 individuals (80%). A PCR signal at baseline existed in 7/18 cases (39%) and HIV DNA at baseline was measured  $\geq 2.7/10^6$  PBMCs among 9/16 individuals (56%) (Table 2).

Univariate and multivariate analysis are shown in Table 2 and Figure 1. Risk factors found to be independently associated with virological failure were a time before first ART  $\geq 90$  days (hazard ratio [HR] 5.16; 95% CI 1.72-15.49), a nadir of CD4 T cells inferior to 350 (HR 12.10; 95% CI 2.31-63.33), when a plasma HIV RNA signal was detected at baseline (HR 4.84; 95% CI 1.67-14.03) and a HIV DNA level at baseline

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$\geq 2.7/10^6$  PBMCs (HR 3.81; 95% CI 1.28-11.37). The multivariate analysis was performed among 164 subjects.

Moreover, no virological failure occurred among the 56 DTG-m participants with a nadir of CD4 T-cell was above  $350/\text{mm}^3$  and when HIV DNA level was below  $2.7/10^6$  PBMCs.

#### ***Effect of DTG-m versus cART on virological failure***

Overall, 16 individuals among 227 (7%) in the DTG-m arm had a virological failure versus none in the cART arm. Time to virological failure was statistically significant different between DTG-m and cART groups according to the Kaplan–Meier curve (Figure 2).

Risk difference (RD) of virological failure between the two arms was significantly different (RD 0.07; 95% CI 0.01–0.12;  $p=0.02$ ). Overall between-studies heterogeneity in the global cohort was  $I^2=51\%$ .

Analyses of the virological failure differences between individuals in the DTG-m arm versus the cART arm for each group of participants found to be at risk of virological failure in the Cox model are shown in Table 3.

We found in the subgroup of participants with a time between HIV diagnosis and first ART  $\geq 90$  days a difference of 10% between the two arms was (RD 0.10; 95% CI 0.01-0.19) and 2% in the subgroup of participants with a time before first ART  $< 90$  days (RD 0.02; 95% CI -0.04-0.08). Heterogeneity was  $I^2=47.2\%$  and the RD was significantly higher among the DTG-m arm when the time before first ART was  $\geq 90$  days,  $p=0.04$  (Supplemental Figure S4). We found in the subgroup of participants with a nadir of CD4 T cells  $<350/\text{mm}^3$  an absolute difference of 8% between

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participants on DTG-m or cART (RD 0.08; 95% CI -0.01-0.17) and 2% in the subgroup of participants with a nadir of  $CD4 \geq 350/mm^3$  (RD 0.02; 95% CI -0.03-0.07). Between the two subgroups of nadir, heterogeneity was  $I^2=29\%$  (Supplemental Figure S5). We found in the subgroup of patients with a detected plasma HIV RNA signal at baseline, an absolute difference of 16% (RD 0.16; 95% CI 0.03-0.30) and 4% in case of absence of PCR signal (RD 0.04; 95% CI 0.01-0.08). Heterogeneity was  $I^2=64.2\%$  and both RD were significantly different with more virological failure in the DTG-m arm than in the cART arm,  $p=0.02$  and  $0.02$  (Supplemental Figure S6). A difference of 32% between the two arms was found in the subgroup of participants with a baseline HIV DNA  $\geq 2,7 \log/10^6$  PBMCs (RD 0.32; 95% CI 0.09-0.56) and 4% in the subgroup of participants with a baseline HIV DNA  $<2.7 \log/10^6$  PBMCs (RD=0.04; 95% CI -0.03-0.11). Heterogeneity was measured  $I^2=80.2\%$  and the RD was significantly higher among the DTG-m arm when baseline HIV DNA  $\geq 2,7 \log/10^6$  PBMCs,  $p=0.007$  (Supplemental Figure S7).

#### **Secondary outcomes**

Amplification for drug resistance testing was successful for 15 of the 18 (83.3%) participants with virological failure. Seven resistance-associated mutations in the integrase gene among the 15 (46.7%) integrase sequencing obtained were found among DOMONO, DOLAM and MONCAY participants plasma at the time of virological failure. The detected mutations were N155H found in 4/15 (26.7%) cases, S147G in 2/15 (13.3%), R263K in 2/15 (13.3%), E138K in 1/15 (6.7%) and S230R in 1/15 (6.7%). Among the 7 participants who were found to have an HIV infection become resistant to INI, none were exposed to any INI before DTG-m. Six had an

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integrase sequencing in plasma at baseline and no resistance-associated mutations in the integrase gene was found.

All DTG plasma concentrations obtained were efficient for DOLAM, DOMONO and EARLY-SIMPLIFIED participants with virological failure. Self-reported adherence was > 95% among DOMONO, DOLAM and MONCAY participants with virological failure. DOLAM, EARLY-SIMPLIFIED and MONCAY participants assigned to DTG-m arm with any adverse event were 146/177 (82.5%) versus 99/144 (68.7%) among participants in the cART arm. Serious adverse events were reported among 17/177 (9.6%) DTG-m participants versus 19/144 (13.2%) among participants in the cART arm. Study drug related adverse effect were found among 15/146 (10.3%) in the DTG-m arm versus 14/113 (12.4%) in the cART arm. Neuropsychiatric effects were reported by 14/99 (14.1%) among DTG-m participants and 2/64 (3.1%) among cART participants. One serious adverse effect related to study drug occurred under DTG (spontaneous abortion). No participant under DTG-m discontinued therapy due to adverse effects.

## **DISCUSSION**

In an IPDMA from four European RCTs, we found a higher risk of virological failure in participants who received DTG-m as a maintenance therapy compared to cART in PLHIV. Among the 272 participants who received DTG-m, 18 (6.6%) underwent a virological failure. The incidence rate of virological failure was estimated at 1.69/1000 persons-years. Participants under DTG-m had an increasing risk of virological failure if the time before first ART was  $\geq 90$  days, the nadir of CD4 T cells was  $< 350/\text{mm}^3$ , when a plasma HIV RNA signal was detected at baseline and when the HIV DNA

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level at baseline was  $\geq 2.7/10^6$  PBMCs. The impact of DTG-m differed consistently across population subgroups according to the time before first ART, plasma HIV RNA signal and HIV DNA level at baseline. The highest risk difference between DTG-m and cART was found when HIV DNA level was  $\geq 2.7 / 10^6$  PBMCs (32%) and moreover, the highest heterogeneity was found in the HIV DNA level subgroup analysis. Indeed, 80.2% of the virological failure risk difference between DTG-m and cART could be explained by HIV DNA level.

A meta-analysis of simplified DTG maintenance therapy found a higher proportion of virological failure 8.9% (95% CI 4.7–16.2%) at weeks 48. (24) In a French retrospective cohort, three virological failure occurred among 61 (4.9%) participants switched to DTG-m and the incidence of virological failure was 2.45 per 100 persons-years at W48. This level is higher than in our study, which can be explained by a previous exposition to INI for all virological failure and an INI resistance-associated mutation at baseline for one virological failure. (31,32) In a German retrospective cohort, one virological failure occurred among 31 (3.2%) individuals followed 24-weeks but we noticed in our study that most virological failure occurred between 24 and 48 weeks. (33) Longer than 48 weeks, virological failure are rare. (24,32)

Participants under DTG-m had a 5 times higher risk of virological failure when time before first ART was  $\geq 90$  days, a 12 times greater risk when nadir of CD4 T cells  $< 350/\text{mm}^3$ , a four times greater risk when a plasma HIV RNA signal was detected at baseline and more than three times in case of a HIV DNA level at baseline  $\geq 2.7/10^6$  PBMCs. Furthermore, we found an absence of virological failure among selected participants with a high nadir CD4 and a low HIV DNA at baseline. Our study, by conducting multivariate analysis, adds to the DOMONO results, the independence of DTG-m virological failure risk factors, which were found to be a higher HIV DNA level

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at baseline, a lower nadir of CD4 T cells and a longer time between HIV diagnosis and start of cART. (28)

The size of the viral reservoir is represented by PCR signal at baseline and HIV DNA level among controlled HIV individuals. (34) The nadir of CD4 T-cell have still been showed as an independent predictor of HIV DNA level after prolonged suppression of viremia, and a longer time between HIV diagnosis and cART initiation as a predictor of an higher HIV DNA level. (35,36) HIV-1 DNA level in participants on successful cART for > 6 months mainly reflects integrated HIV-1 DNA and low levels were associated with low risks of disease progression, viral rebound and drug resistance. (37) Further than previous studies on DTG-m virological failure risk factors, we are able to conclude to an independent association between a higher HIV DNA level at baseline and virological failure, and between a lower nadir of CD4 T cells and virological failure. A higher HIV DNA level at baseline and a lower nadir of CD4 T cells were also previously described as risk factors for virological failure during PI monotherapy. (38–40)

Thus, our study showed the viral reservoir as the key determinant of viral escape under monotherapy. The reactivation of HIV from latently infected cells depends on the size of the replication-competent viral reservoir. A higher HIV DNA level led to a higher risk of reactivation of pre-existing provirus harboring a single mutation associated with integrase inhibitor resistance. In EARLY-SIMPLIFIED trial, only one virological failure occurred and he did not fulfill primary HIV infection definition. The small genetic diversity of HIV in the primary infection and a preserved immune system may explained EARLY-SIMPLIFIED results. (41,42)

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No virological failure could be explained by DTG plasma concentration, which all were found to be adequate when evaluated. Adequate DTG plasma concentrations with and without virological failure is consistent with previous studies which did not identify lower plasma concentrations as a risk factor for virological failure, confirming the robustness of the DTG. (18,31,43) Hypothesis of a differences in drug concentration between plasma and sanctuary sites was explored in EARLY-SIMPLIFIED trial. (25) All the DTG level measured in the CSF in a subset of participants at baseline and at week 48, exceeded the in vitro IC 50 for wild-type HIV-1 and achieved therapeutic concentrations in the CNS. Various PI monotherapy studies identified suboptimal adherence as a risk factor for virological failure. (40,43) No virological failure could be explained by suboptimal adherence, which was found to be high in all RCTs.

Almost half of participants who underwent a virological failure developed a resistance-associated mutations in the integrase gene at the time of virological failure. This result is consistent with the previous meta-analysis. (24) In the French cohort study, all the three virological failure under DTG-m had emergence of INI resistance, explained by the previous exposition to INIs and INI resistance-associated mutation detected for one patient. (32) It did not occur among participant of our IPDMA. The most detected mutation found in our IPDMA was N155H, then S147G, R263K, E138K and S230R. Regarding the good adherence and adequate DTG plasma concentration, a single INSTI-RAMs seems sufficient to cause virological failure in patients receiving DTG-m maintenance. Moreover, de novo mutations suggest cross-resistance to other available or future INI. Our results showed that the genetic barrier to resistance of DTG is insufficient in monotherapy.

In another way, half of the virological failure did not develop a resistance-associated mutation in the integrase gene. DOMONO team hypothesized in a resistance dynamics

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study that a stochastic reactivation of a single cell harboring a provirus with an INSTI-RAM or mutations in the G stretch of the 3'-PPT region could explain a part of the DTG-m virological failure. (44) The large variation in the time to virological failure observed in our IPDMA play in favour of this hypothesis.

Our study presented several strengths and limitations. All RCTs published evaluating DTG-m were included which resulted in an important data collection. An IPDMA could be done thanks to the similar methodology of RCTs. All were randomized, multicentric open-label non inferiority trials. Homogeneity of the primary efficacy endpoint was allowed by the IPDMA. We expose long-term data (48 weeks) which is necessary regarding the mean time of virological failure. Even if incidence of virological failure was low, we could analyze and published the first multivariate model of virological failure risk factors under DTG-m.

The first limitation is the absence of virological failure in the controlled group which gave not available a Cox model to analyse heterogeneity of studies. We have not validated our results in a separate cohort. Then, only European studies could be included in the IPDMA which wonder the generalization of results. We have a lack of HIV DNA level at baseline and we only have two HIV DNA level at the time of virological failure in our IPDMA. In observational studies, median HIV DNA did not change significantly between baseline and at week 48. (32,45) It suggests that the HIV-1 latent reservoir did not replenished on DTG-m. Finally, regarding safety of the DTG, we did not give data about weight during follow-up nore change in visceral or subcutaneous adipose tissues. (19,46–48)

We assessed the safety of DTG by evaluating the frequency of serious adverse events and events related to study drug. Both were found rarely and less frequently



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among participants in the DTG-m group than in the controlled group. No participant under DTG-m discontinued therapy due to adverse effects. Neuropsychiatric effect was the most frequently adverse effect reported which is consistent with previous studies evaluating DTG in monotherapy. (32,45)

The last update of EACS guidelines recommends DTG based bithérapie as a maintenance therapy. (2) Some patients sometimes present with a resistant HIV infection or medical conditions which reduce possibilities of treatment. Monotherapy or functional monotherapy could be an option among selected patients. Our study showed that DTG-m do not lead to virological failure after 48 weeks among PLHIV with a high nadir CD4 and a low HIV DNA. In a trithérapie second generation INI-based RCT, individuals under DTG plus emtricitabine and tenofovir alafenamide did not present a significant difference in virological efficacy with or without prior NRTI resistance, 97% and 94% if M184V/I versus 89% and 91%. (46) The SWORD study results indicate that dolutegravir-rilpivirine maintained HIV-1 suppression with no increased risk of developing resistance. (14) Six among 11 individuals who experienced virological failure developed resistance to RPV and none to DTG. The TANGO study observed no failure among four individuals found to have a M184V/I mutation. (17) In recent retrospective study, among 19 DTG functional monotherapy and 20 on DTG functional dual therapy, a persistent virological failure > 50cp/mL were observed respectively in 2 (11%) and 5 (25%) participants. (49) Authors explained virological failure because of a suboptimal adherence.

The World Health Organization (WHO) recommended DTG-based regimen in second line of treatment. (50) In low income countries, a high prevalence of NRTI resistance and M184V/I mutation have been demonstrated with a high virological outcome among individuals treated with DTG-based regimens. (51–54) In the DAWNING study, 16%

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(51/312) of those in the DTG arm did not achieve viral suppression whereas 84% (261/312) had a baseline M184V/I. (52)

In conclusion, our IPDMA illustrated the need to explore HIV DNA level before ART simplification strategies decreasing the burden of antiretroviral therapy such as DTG-m and to be careful in case of a long time  $\geq 90$  days between HIV diagnosis and first ART, a nadir of CD4 T-cell  $< 350/\text{mm}^3$  or a HIV RNA PCR signal or a HIV DNA level  $\geq 2.7 / 10^6$  PBMCs among patients under monotherapy or functional monotherapy of DTG. Major issue was the development of drug resistance mutations to DTG in case of virological failure which reduce future treatment options. Otherwise, we found an absence of virological failure among selected participants with no previous virological failure, no previous INI exposition, at least 6 months with controlled VL, a high adherence to ART, a high nadir CD4 and a low HIV DNA at baseline which could allow a functional monotherapy. Detectability of HIV RNA, quantification of HIV DNA and knowledge of the time before first ART and nadir of CD4 T-cell prior to the simplification of treatment should help physicians in selecting candidates for a DTG-m.

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Table 1. Baseline demographic and clinical characteristics of individual patients' data in dolutegravir monotherapy (DTG-m) group and combined antiretroviral therapy (cART) group

<b>Risk factors</b>	<b>Overall N=416</b>	<b>DTG-m N=227</b>	<b>cART N=189</b>	<b>p***</b>	
<b>Male, n(%)</b>	354 (85.1%)	197 (86.8%)	157 (83.1%)	0.29	
<b>Age at baseline, mean (SD)</b>	46 (12)	45 (12)	47 (12)	0.19	
<b>Ethnicity, n(%)</b>					
	White	361 (86.8%)	199 (87.7%)	162 (85.7%)	
	Black	42 (10.1%)	23 (10.1%)	19 (10.1%)	0.52
	Other	13 (3.1%)	5 (2.2%)	8 (4.2%)	
<b>Time before first ART (days)*, median (IQR)</b>	91 (30.4-759)	72 (29-547)	133 (33-863)	0.11	
<b>HIV transmission group*, n(%)</b>					
	Men who have sex with men	288 (69.4%)	159 (70.0%)	129 (68.6%)	
	Heterosexual	98 (23.6%)	54 (23.8%)	44 (23.4%)	0.77
	Other	29 (7.0%)	14 (6.2%)	15 (8.0%)	
<b>BMI (kg/m) at baseline, mean (SD)</b>	24.8 (3.7)	24.8 (3.7)	24.7 (3.8)	0.79	
<b>INI 1st generation exposure, n(%)</b>	60 (14.4%)	27 (11.9%)	33 (17.5%)	0.11	
<b>Previous genotypic resistance to any integrase strand transfer inhibitor*, n(%)</b>	5 (2.3%)	3 (2.6%)	2 (2.0%)		
<b>Presence of a plasma HIV RNA signal at baseline**</b>	72 (17.4%)	38 (16.7%)	34 (18.1%)	0.72	
<b>CD4-T cells count at baseline (/mm<sup>3</sup>), mean (SD)</b>	777 (284)	786 (276)	767 (294)	0.49	
<b>Zenith Viral load (copies/mL)**, mean (SD)</b>	213,436 (649,766)	287,016 (871,231)	137,481 (257,633)	0.07	
<b>Nadir CD4-T cells count (/mm<sup>3</sup>), mean (SD)</b>	362 (178)	368 (178)	354 (179)	0.43	
<b>HIV DNA at baseline (log/10<sup>6</sup> PBMCs)**, mean (SD)</b>	2.33 (0.45)	2.38 (0.43)	2.25 (0.47)	<b>0.04</b>	

\* Presence of missing data (between <1% and 15%)

\*\* Presence of missing data (between 25% and 49%)

\*\*\*p-value represents comparison between DTG-m and cART groups

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Table 2. Description and Cox model of factors associated with virological failure among subjects randomized to dolutegravir monotherapy (DTG-m), N=165.

Risk factors	No virological failure N=254	Virological failure N=18	Univariate analysis Hazard ratio (95%CI)	p- value	Multivariate analysis*** Hazard ratio (95%CI)	p- value
<b>Gender, n(%)</b>						
Male	221 (87.0%)	18 (100%)	1	0.09*		
Female	33 (13.0%)	0 (0%)	NA			
<b>Age at baseline, mean (sd)</b>	45 (12)	50 (11)	1.04 (1.01-1.08)	<b>0.05</b>		
<b>Ethnicity, n(%)</b>						
White	219 (86.2%)	15 (83.3%)	1	0.58*		
Black	27 (10.6%)	3 (16.7%)	1.62 (0.47-5.59)			
Other	8 (3.2%)	0	NA			
<b>Time before first ART (days)<sup>1</sup>, n(%)</b>						
< 90	117 (52.0%)	3 (20.0%)	1	<b>0.008</b>	1	<b>0.003</b>
≥90	108 (48.0%)	12 (80.0%)	4.62 (1.30-16.38)		5.16 (1.72-15.49)	
<b>HIV transmission group, n(%)</b>						
Men who have sex with men	182 (71.7%)	12 (66.7%)	1	0.94		
Heterosexual	56 (22.0%)	5 (27.8%)	1.21 (0.43-3.43)			
Other	16 (6.3%)	1 (5.5%)	0.96 (0.13-7.40)			
<b>Nadir CD4-T cells count (/mm<sup>3</sup>), n(%)</b>						
<350	133 (52.4%)	15 (83.3%)	4.23 (1.22-14.60)	<b>0.009</b>	12.10 (2.31-63.33)	<b>0.003</b>
≥350	121 (47.6%)	3 (16.7%)	1		1	
<b>Presence of a plasma HIV RNA signal at baseline<sup>1</sup>, n(%)</b>						
Yes	39 (15.4%)	7 (38.9%)	3.38 (1.31-8.71)	<b>0.02</b>	4.84 (1.67-14.03)	<b>0.004</b>
No	214 (84.6%)	11 (61.1%)	1		1	
<b>CD4-T cells count at baseline (/mm<sup>3</sup>), mean (sd)</b>	779.2 (273.9)	742.2 (233.2)	0.97 (0.88-1.06)**	0.47		
<b>HIV DNA at baseline (log/10<sup>6</sup> PBMCs)<sup>2</sup>, n(%)</b>						
<2.7	128 (85.9%)	7 (43.7%)	1		1	

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	≥2.7	21 (14.1%)	9 (56.3%)	6.01 (2.24-16.15)	<0.001	3.81 (1.28-11.37)	<b>0.02</b>
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(Table 2 suite)

NA : non applicable

\*: log-rank test

\*\* : HR represents an increase of 50 cells

\*\*\*: HIV transmission group variable did not met the proportional risk hypothesis.

<sup>1</sup> Presence of missing data (between <1% and 11%)

<sup>2</sup> Presence of missing data (between 38% and 41%)

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Table 3. Heterogeneity in subgroup analyses of the virological failure difference between participants on dolutegravir monotherapy (DTG-m) or combined antiretroviral therapy (cART).

	m-DTG (n/N)	cART arm (n/N)	D [95%CI]	p-value	subgroup I <sup>2</sup>
Time before first ART ≥90 days	10/87	0/93	0.10 (0.01; 0.19)	0.04	47.2%
Time before first ART <90 days	3/108	0/65	0.02 (-0.04; 0.08)	0.47	
Nadir CD4 <350/mm <sup>3</sup>	13/129	0/114	0.08 (-0.01;0.17)	0.08	29.0%
Nadir CD4 ≥350/mm <sup>3</sup>	3/98	0/75	0.02 (-0.03;0.07)	0.52	
Presence of a plasma RNA signal at baseline	7/38	0/34	0.16 (0.03; 0.30)	0.02	64.2%
Absence of a plasma RNA signal at baseline	9/189	0/154	0.04 (0.01; 0.08)	0.02	
HIV DNA at baseline ≥2,7 log/10 <sup>6</sup> PBMCs	9/27	0/10	0.32 (0.09;0.56)	0.007	80.2%
HIV DNA at baseline <2.7 log/10 <sup>6</sup> PBMCs	5/106	0/70	0.04 (-0.03; 0.11)	0.22	

95% CI: 95% confidence interval; D: risk difference

Data NA: nadir CD4 (n=0), HIV DNA (n=203), PCR signal (n=1), Time before ART (n=63)

n: number of virological failure ; N: number of patients

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Figure 1. Distributions of A. CD4 T-cell nadir, B. baseline HIV1 DNA copy number in peripheral blood mononuclear cells (PBMCs), C. Time before first antiretroviral therapy after HIV diagnosis (days), D. Presence of a plasma HIV RNA signal at baseline in patients, with and without virological failure during dolutegravir monotherapy (DTG-m).

Figure 2. Incidence and risk difference of virological failure between dolutegravir monotherapy (DTG-m) and combined antiretroviral therapy (cART)

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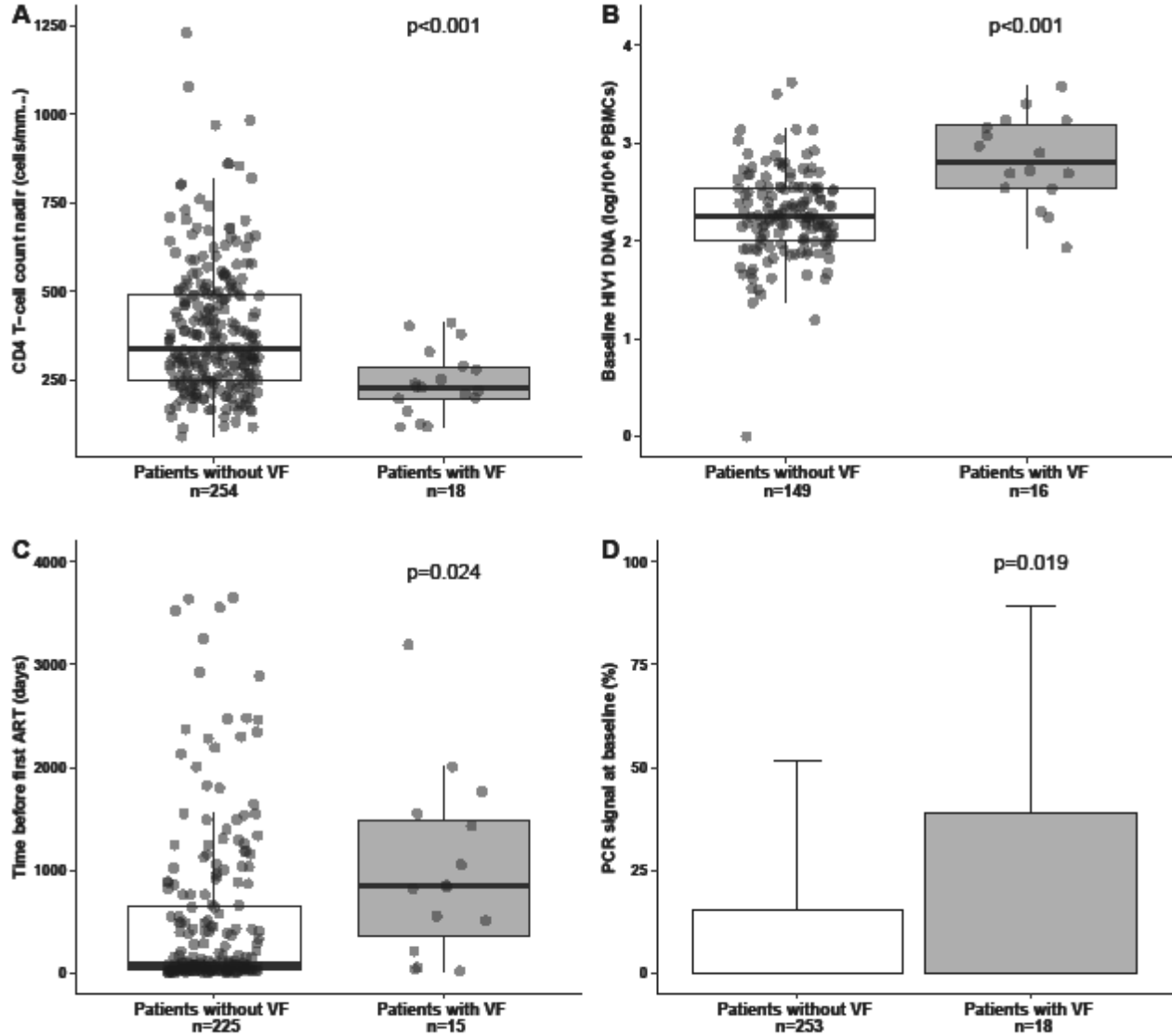
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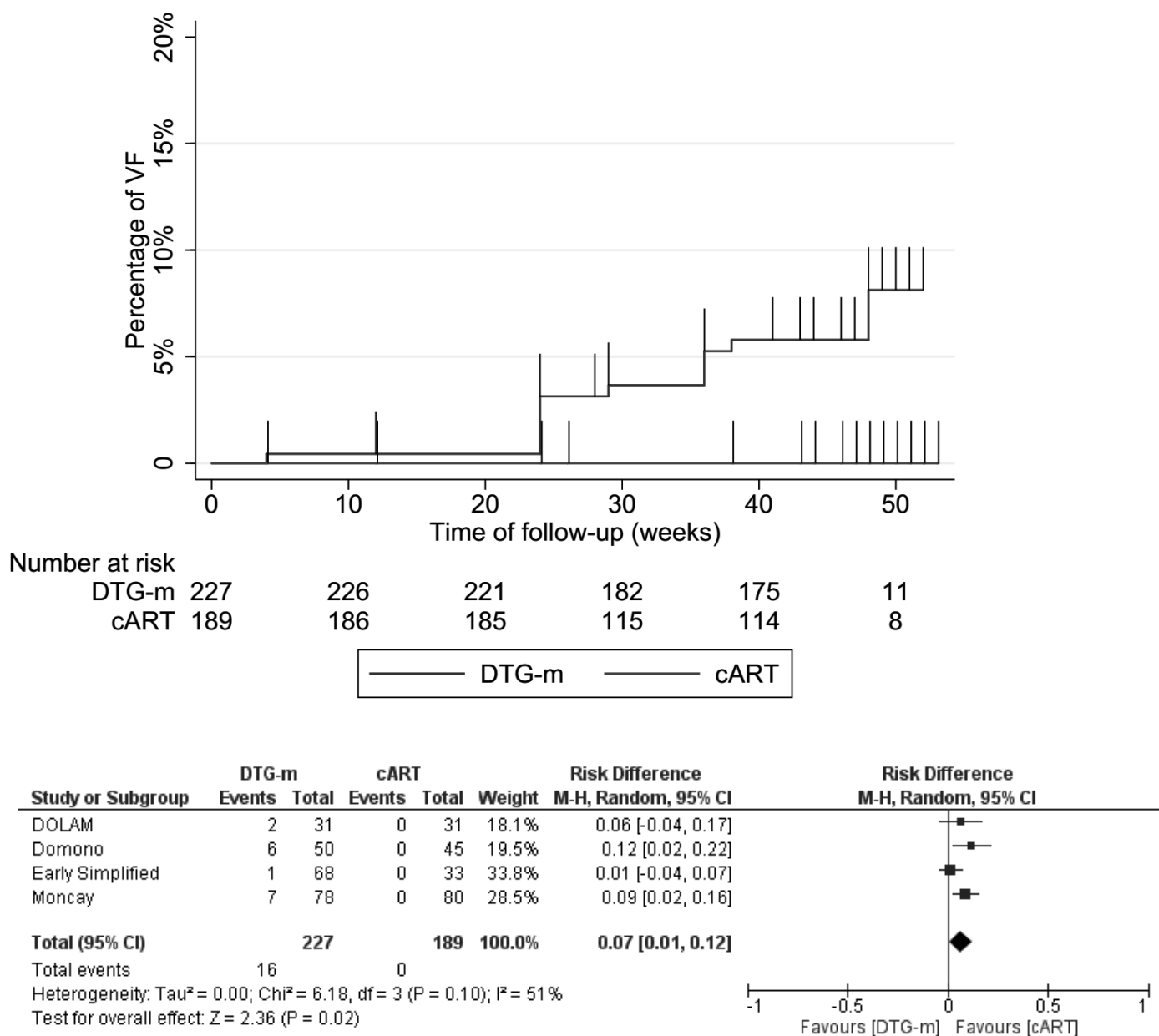
IV. Facteurs associés à l'échec virologique sous dolutegravir en monothérapie

Figure 1.



#### IV. Facteurs associés à l'échec virologique sous dolutegravir en monothérapie

Figure 2.



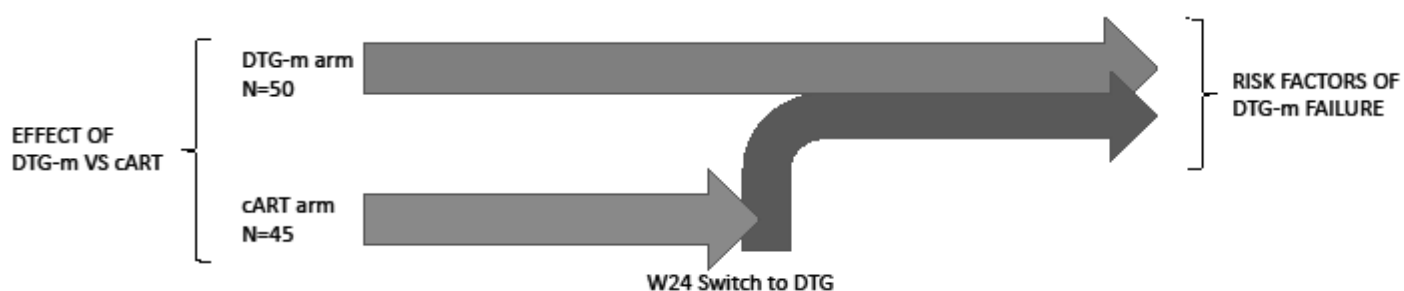
## SUPPLEMENTAL APPENDIX

Table S1. Characteristics of included studies.

Trials	Early-Simplified	DOMONO	DOLAM	MONCAY
<b>Country</b>	Switzerland	Netherlands	Spain	France
<b>Patients included</b>	101	95	62	158
<b>DTG-m arm (N)</b>	68	50	31	78
<b>cART arm (N)</b>	33	45	31	80
<b>Mean age (years; SD)</b>	41 (11)	46 (11)	47 (12)	48 (12)
<b>Sex ratio</b>	24.2 (97/4)	12.6 (88/7)	7.9 (55/7)	2.6 (114/44)
<b>Mean CD4 (cells/mm<sup>3</sup>; SD)</b>	772 (263)	714 (230)	733 (338)	835 (295)
<b>Mean HIV DNA (/10<sup>6</sup> PBMCs; SD)</b>	2.27 (0.24)	2.20 (0.53)	NA	2.76 (0.43)
<b>Nadir CD4 (cells/mm<sup>3</sup>; SD)</b>	384 (167)	409 (187)	331 (142)	331 (186)

*DTG-m : monotherapy of Dolutegravir; cART : combined antiretroviral therapy; VF: virological failure; VL: viral load  
NA: Not available*

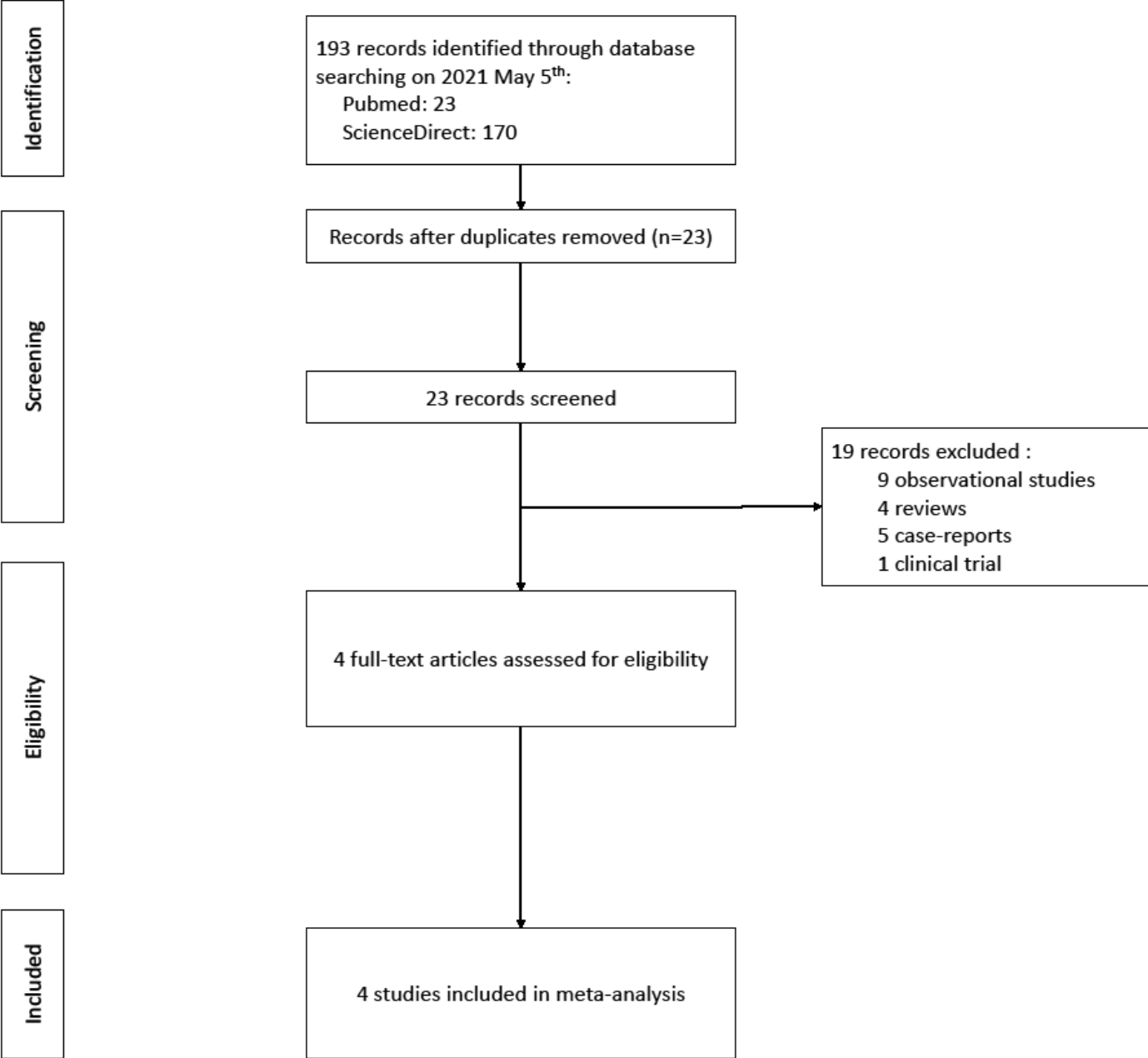
Figure S1. DOMONO study design and IPDMA.





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Figure S2. Flowchart.



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Figure S3. Prisma quality of studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
DOLAM	+	+	-	-	+	+	+
Domono	+	+	-	-	+	+	+
Early Simplified	+	+	-	+	+	+	+
Moncay	+	+	-	-	+	+	+

#### IV. Facteurs associés à l'échec virologique sous dolutegravir en monothérapie

Figure S4. Risk differences and heterogeneity with forest plot according to time before first antiretroviral therapy after HIV diagnosis.

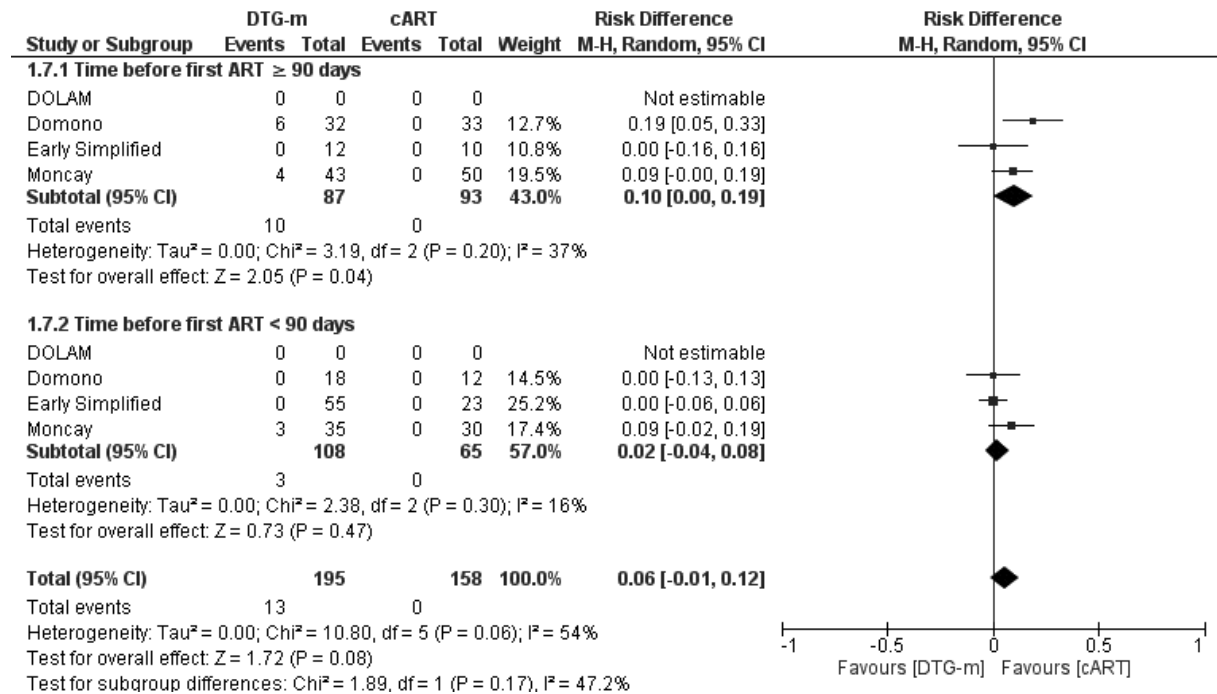
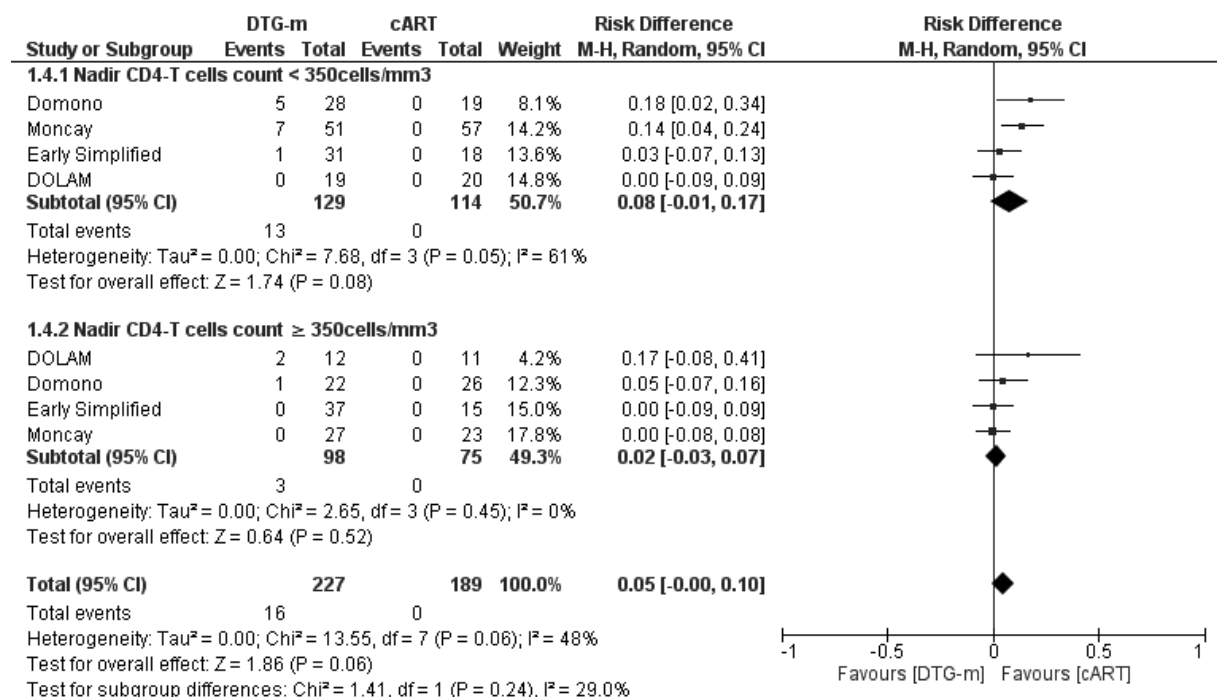


Figure S5. Risk differences and heterogeneity with forest plot according to nadir of CD4-T cells count.



#### IV. Facteurs associés à l'échec virologique sous dolutegravir en monothérapie

Figure S6. Risk differences and heterogeneity with forest plot according to plasma HIV RNA signal at baseline.

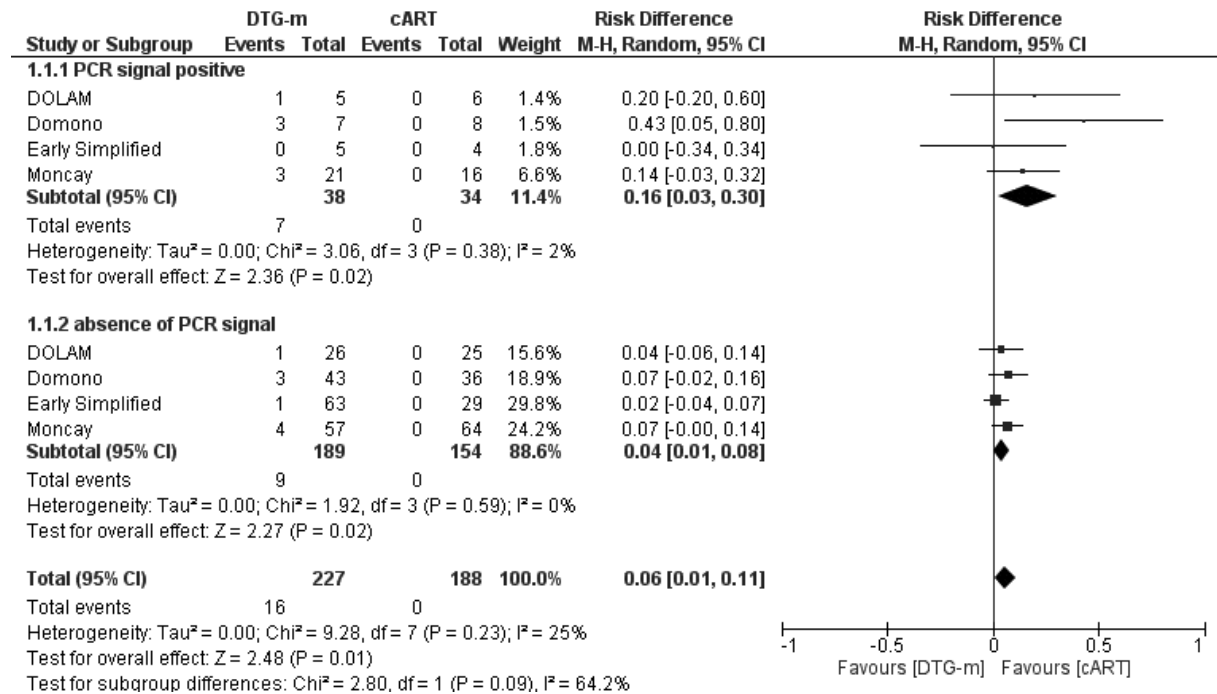
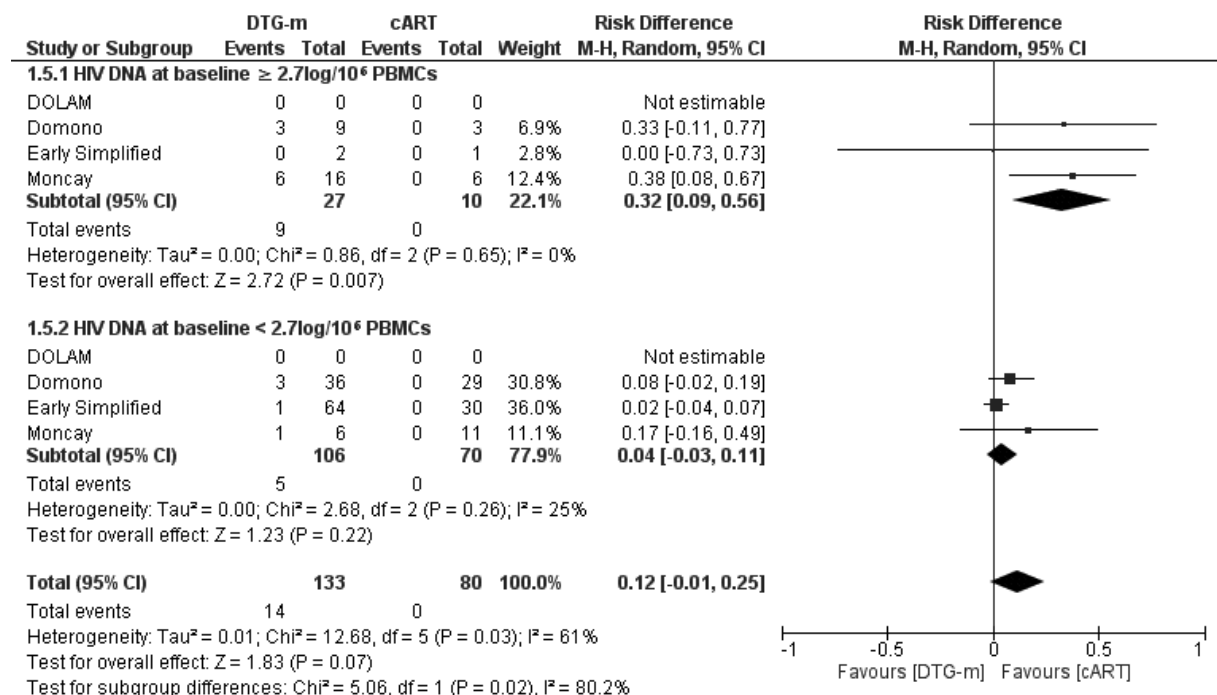


Figure S7. Risk differences and heterogeneity with forest plot according to HIV DNA at baseline.



#### IV. Facteurs associés à l'échec virologique sous dolutegravir en monothérapie

## V. DISCUSSION

### a) **Importance des caractéristiques individuelles dans la rétention dans le soin**

Parmi les 4 796 PVVIH suivies dans le SMIT de l'hôpital Bichat entre 2010 et 2016, le taux d'incidence de rupture de soin  $\geq 18$  mois fut estimé à 2,5 pour 100 p-a dans la cohorte de Bichat et à 3,0 pour 100 p-a dans la cohorte de Caen (Publications n<sup>os</sup> 1 et 2).

Dans la cohorte de Bichat, nous avons trouvé 617 (13%) patients avec une ISM et parmi eux, 214 (35%) sont revenus dans le service. Les facteurs indépendants augmentant le risque d'ISM étaient : ne pas avoir de médecin traitant, un temps avant la prise en charge du VIH  $> 6$  mois après le diagnostic, habiter le 18<sup>e</sup> arrondissement de Paris, un taux de lymphocytes CD4  $\leq 350/\text{mm}^3$ , et ne pas être sous ART pendant le suivi. Être né en ASS était associé à un plus faible risque.

Dans la cohorte de Caen, nous avons trouvé 144 (15%) patients avec une ISM dont 35 (24%) avec un retour dans le soin. Les facteurs significativement associés à l'ISM étaient au moment du diagnostic du VIH : être né en ASS, un temps avant la prise en charge du VIH  $> 6$  mois après le diagnostic, la co-infection VHC et ne pas avoir fourni une adresse postale. Au cours du suivi, ne pas être sous ARV était un FDR d'ISM et être âgé de plus de 45 ans, un facteur protecteur.

La méthodologie employée pour rechercher le devenir des patients prétendus PDV est une des forces majeures de notre étude. En effet, nous avons pu recueillir des informations (déménagement, suivi ailleurs, décès) chez 322 patients suivis à Bichat et 96 à Caen considérés à tort en ISM par notre requête informatique. Ces informations furent apportées majoritairement grâce à l'interrogatoire des infectiologues référents (56% à Bichat et 71% à Caen), et après consultation des dossiers médicaux (42%). L'appel du médecin traitant a contribué très faiblement dans la recherche à Bichat (2%) mais fut plus contributif à Caen (29%). Une autre force est le faible taux de données manquantes, un maximum de 10 % pour la variable lieu de

## V. Discussion

résidence dans la cohorte de Caen et 12% pour la variable mode de contamination dans la cohorte de Paris.

Nous avons recherché activement les patients avec ISM, ce qui réduit le biais de classification. Cependant, nous n'avons pas eu d'information pour 81/617 (13%) cas d'ISM à Bichat et 13/144 (9%) ISM à Caen. Ceci a pu conduire à une surestimation du taux d'incidence si ces patients étaient partis ailleurs ou décédés. Nous n'avons pas pu consulter le registre national des décès ni des écrous pour ces patients. Cette limite semble faible devant la rentabilité quasi-nulle de la recherche de statut vital réalisée par Ndiaye et al. en France entre 1997 et 2006. En effet, seulement 2 patients sur 1007 étaient considérés PDV à tort après consultation des registres (47).

En France, peu d'études ont été menées pour définir le profil des PVVIH en rupture de suivi. Le taux d'incidence varie selon les études entre 3,5 et 17,2 per 100 p-a (8,47–49). Le taux le plus élevé était en Guyane où il existe un manque de structure de soins, une précarité et une stigmatisation persistante des PVVIH (48). On constate une proportion plus importante de PDV dans les études se déroulant au début des années 2000 (13.4%) comparativement à 2013 (8.5%) (8,47,50). Notre période d'étude est située après d'important progrès dans la prise en charge du VIH au niveau de l'efficacité et de la tolérance des ARV. La faible incidence d'ISM dans nos deux cohortes peut être expliquée par notre définition d'ISM qui est moins stricte que celle des autres études. Nous avons considéré comme nécessaire d'avoir une approche différente de la rétention, définie jusqu'alors comme un patient régulièrement vu en consultation avec son infectiologue. Dans une étude américaine, parmi 17 140 personnes suivies entre 2010 et 2012, 10% étaient considérées comme mal suivies malgré une CV indétectable (51). Ces patients étaient non suivis par leur infectiologue mais peut-être par un médecin de ville ou ailleurs et donc bien contrôlés. C'est pourquoi notre définition de patient suivi incluait les patients n'ayant pas vu leur infectiologue pendant 18 mois, mais ayant vu leur médecin traitant, eu un bilan immuno-virologique, ou revenant avec une CV indétectable.

De plus, le taux faible de perte de vue de nos deux cohortes peut être expliqué par une prise en charge compréhensive des patients. Les SMIT de l'hôpital Bichat et de Caen bénéficient d'une équipe pluri-disciplinaire avec des infectiologues spécialisés, du personnel paramédical formé en éducation thérapeutique, des assistantes sociales pour faciliter les démarches administratives, et des associations qui favorisent l'éducation des patients et encouragent une bonne prise en charge.

## V. Discussion

Nous avons retrouvé une incidence d'ISM au cours de notre étude significativement plus faible dans la cohorte suivie à Bichat comparée à Caen. Les deux SMIT ont mis en place le rappel des rendez-vous la veille par SMS mais seul le SMIT Bichat propose des visites médicales sans rendez-vous avec un infectiologue. Cuzin et al. ont exposé dans une récente étude, l'hétérogénéité de la rétention dans le soin entre 7 centres hospitaliers français, avec une proportion d'ISM allant de 8,7% à 19,7% (8). Ceci peut être expliqué par des populations suivies différentes mais aussi l'offre de soin différente.

Ne pas avoir de médecin traitant était retrouvé comme un important FDR d'ISM dans la cohorte parisienne, en accord avec l'étude de Ndiaye et al. (HR=1,76; IC95%=1,05-2,96). Le lien entre l'infectiologue à l'hôpital et le médecin traitant est crucial pour assurer la continuité des soins et retirer la barrière structurelle hospitalière (52). Un envoi automatique des courriers médicaux entre les médecins pourrait améliorer le suivi des patients (53,54).

Ne pas avoir d'adresse postale dans le dossier médical était associé à un risque significativement plus important d'ISM pour la cohorte de Caen. On peut se demander si les patients sans adresse renseignée (10% à Caen et 20% à Bichat) sont sans domicile fixe. Ce facteur était retrouvé comme à risque de perte de vue dans l'étude de Lebouché et al. publiée en 2006, parmi 1 786 PVVIH suivies à Tourcoing, les personnes sans domicile fixe avaient un risque plus élevé d'ISM (HR=2,2; IC95%=1,0-4,9) (49).

Un premier rendez-vous tardif entre le diagnostic du VIH et sa prise en charge, et ne pas être traité par ARV au cours du suivi, furent retrouvés comme des FDR importants d'ISM dans nos deux cohortes. Le traitement représente un lien entre le patient et le système de soins (10). Les recommandations actuelles sont en faveur d'un traitement ARV précoce, mais la majorité des patients de notre étude avait reçu une première ligne de traitement ARV plus d'un an après leur diagnostic de VIH (54% à Bichat et 61% à Caen) (10).

Dans la cohorte de Caen, avoir plus de 45 ans au cours du suivi était un facteur protecteur d'ISM. Ce FDR est souvent retrouvé dans la littérature (8,47,49,55,56). Le mode de vie des patients de  $\leq 30$  ans, les relations conflictuelles liées à l'adolescence et une stigmatisation plus importante de l'individu malade jeune sont des barrières à un suivi médical régulier (57). Améliorer la rétention des patients les plus jeunes est un enjeu de santé publique important, au niveau individuel par le nombre d'années de vie gagnées et au niveau collectif par le risque de transmission du VIH induite par l'activité sexuelle des personnes  $\leq 30$  ans (58,59).



## V. Discussion

La co-infection VHC au moment du diagnostic du VIH était également retrouvée comme FDR dans la cohorte de Caen et n'était pas associée à l'ISM dans la cohorte de Bichat, même en analyse univariée. Un manque de puissance statistique est peut-être en cause car la proportion de patient suivi pour une hépatite C au diagnostic était plus faible à Bichat (6% versus 10% à Caen).

Une association entre le bilan immuno-virologique et l'ISM fut retrouvée au cours du suivi de la cohorte de Bichat. Les patients les plus immunodéprimés (avec un taux bas de lymphocytes CD4) pendant leur suivi étaient plus à risque d'ISM. Ce résultat retrouvé dans d'autres études internationales, s'explique par le défaut d'observance au traitement ARV (suivi d'une chute du taux de lymphocytes CD4) qui précède la perte d'adhésion aux soins (47,50,55). D'autre part, l'absence de taux de lymphocytes CD4 lors d'une consultation était associée à un plus grand risque d'ISM. Au vu de la significativité de cette classe « données manquantes », nous pouvons conclure qu'il existait un risque d'ISM significatif lorsque le bilan immuno-virologique n'était pas réalisé. Monitorer les bilans sanguins pour refléter la rétention dans le soin fut évalué avec une sensibilité de 90% (IC95%= 87-94%) (60).

Le pays de naissance était retrouvé comme une variable associée à l'ISM mais dans un sens opposé entre Caen et Bichat, puisqu'être né en ASS comparativement à être né en France était un FDR pour Caen et un facteur protecteur pour Bichat. La proportion de patients nés en dehors de la France était plus grande dans la cohorte de Bichat (62%), beaucoup plus que dans la cohorte caennaise (19%) ainsi que dans la cohorte FHDH (22%) qui comprenait 34 885 patients pris en charge entre 2008 et 2010 (50). Il existait notamment dans la cohorte de Bichat une part importante de personnes nées en ASS (40%). Plusieurs études retrouvent que les patients nés en ASS sont plus à risque de perte de vue (47–50). Par exemple, Ndiaye et al. ont retrouvé un risque de PDV près de 2 fois plus grand entre les patients nés en ASS versus en France (HR=1,81; IC95%=1,16-2,80) (47). Les auteurs expliquent que les immigrés sont géographiquement mobiles et qu'il existe une plus grande proportion d'ISM sans retour dans le soin parmi eux. Or, dans la cohorte de Bichat, il y avait la même proportion de ruptures de suivis avec retour dans le soin et sans parmi les personnes nées dans un pays d'ASS (36%).

Le SMIT de Bichat s'occupe depuis longtemps d'une part importante des immigrés vivant dans le 18<sup>e</sup> arrondissement de Paris. La prise en charge adaptée, les associations de patients et les patients d'origine africaine eux-mêmes ont pu améliorer la rétention dans le soin de ces patients considérés à risque dans le passé ou ailleurs. De plus, les migrants peuvent obtenir l'Aide

## V. Discussion

Médicale d'État (AME) et bénéficiaire de la Permanence d'Accès aux Soins de Santé (PASS) depuis 1998 (Art. L. 711-7-1 du Code de la Santé Publique) (61). Des études complémentaires sont nécessaires pour comprendre le rôle du statut légal des migrants dans la rétention.

Nous avons également retrouvé une hétérogénéité géographique parmi les personnes ayant interrompu leur suivi. Comparé aux habitants d'Île-de-France, hors Paris, les habitants du 18<sup>e</sup> arrondissement de Paris étaient plus à risque d'ISM. Les personnes vivant dans le 18<sup>e</sup> arrondissement, le plus proche mais aussi le plus pauvre de Paris, sont peut-être dans une situation de précarité différente qu'en banlieue, avec des migrants illégaux et des personnes sans domicile fixe. Pour comprendre cette hétérogénéité géographique, nous avons étudié le lien entre l'environnement socio-économique et l'ISM par une revue de la littérature. Un faible revenu (< 10 000 dollars/an) fut retrouvé comme FDR d'interruption de suivi ( $p < 0,001$ ) (62). Mais la précarité ne se résume pas au salaire. Goswami et al., ont étudié parmi les PVVIH d'Atlanta, l'association entre certains déterminants sociaux et la rétention dans le soin. Ces auteurs ont utilisé un indice de déprivation écologique « ZIP code tabulation area) construit à partir du niveau d'éducation, des revenus, du score de Gini (mesure statistique de dispersion représentant les revenus des habitants), la possession d'un téléphone et l'accès aux transports. Dans les zones les plus pauvres, posséder une voiture était associée avec une meilleure rétention (OR=0,16 ;  $p=0,02$ ). Une augmentation de 10% de personnes propriétaires de voiture était associée à une diminution de 30% de la CV ( $p=0,01$ , OR=0,08) (63).

Puis, nous avons pu étudier l'IED dans nos deux cohortes. Nos travaux ont mis en évidence une grande déprivation dans les deux cohortes mais plus importante à Bichat. Nous n'avons pas retrouvé d'association significative entre l'ISM et l'indice de déprivation pour la cohorte parisienne, et une association dans la cohorte caennaise en analyse univariée seulement. Nos résultats sont cohérents avec le travail de Gueler et al., qui ne retrouvait pas d'association entre l'ISM et un indice de déprivation ( $p=0.28$ ) (64). En revanche, il retrouvait une association forte entre le quintile des plus défavorisés et un taux de CD4 bas au moment du diagnostic ( $p < 0.001$ ) ainsi qu'avec le stade CDC ( $p=0.006$ ). Une absence d'association entre le retard au diagnostic et l'IED fut décrite dans une cohorte française prospective (65). Les critères socio-économiques liés aux interruptions de soins semblent être individuels et non liés à l'environnement.

Les interventions pour améliorer la rétention des PVVIH devraient cibler les patients identifiés à risque d'ISM et les barrières qu'ils rencontrent au cours du suivi médical. Les raisons d'ISM

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évoquées sont : manque de temps libre, peur de la stigmatisation, obligations familiales, manque de transport, difficulté d'obtenir un rendez-vous mais aussi, oubli des rendez-vous (66,67). Nos deux études ont mis en avant l'importance de réduire le temps avant la prescription du premier traitement ARV. Nous devons considérer tous ces problèmes pour mettre en place les interventions appropriées et améliorer la rétention des patients.

### **b) Importance de caractériser l'adhésion thérapeutique pour le choix du traitement antirétroviral**

Dans la cohorte DOLUTECAPS (Publication n° 3), les composantes du modèle d'adhésion thérapeutique, Adh-m et ITmax n'étaient pas prédicteurs de la réplication virale. En revanche, il existait une forte association entre le modèle d'adhésion et le niveau de la CV pour les régimes plus anciens, à base de raltégravir, INNTI et IPb. De plus, le traitement par DTG était significativement meilleur que les autres stratégies ARV étudiées en termes de suppression virologique chez les PVVIH du sous-groupe à faible adhésion, indépendamment de l'âge, du sexe, du taux de CD4 et de l'histoire thérapeutique (initiation, changement et échec). Aucune émergence de mutation conférant une résistance aux INI n'a été détectée dans le groupe DTG en cas de CV détectable, contrairement au groupe raltégravir.

Ces résultats suggèrent que les régimes à base de DTG sont plus tolérants aux doses manquées que les autres ARV étudiés, que ce soit des doses manquées par défaut d'Adh-m ou par IT. Des études précédentes ont tenté d'identifier un seuil d'adhésion requis pour la suppression virologique. Par exemple, *Byrd et al.* ont rapporté qu'une Adh-m de 82 % était nécessaire pour la suppression virologique de 90 % des patients traités (68), avec une différence en fonction de la classe thérapeutique : une Adh-m de 75% permettait le contrôle virologique sous INI. En concordance avec les études antérieures, nous retrouvons dans notre analyse multivariée un niveau d'Adh-m < 80 % (68–70) et la durée d'interruption du traitement comme FDR indépendant de la réplication virale, affirmant l'importance de ces deux composantes de l'observance (14,71,72).

Dans le groupe de participants avec une Adh-m  $\leq$  95%, le traitement ARV à base de DTG était significativement et indépendamment associé à un risque moindre de réplication virale par rapport aux autres ARV. Bien que les IC95% étaient importants en raison de la plus petite taille de l'échantillon dans ce sous-groupe, cette supériorité est cohérente avec une méta-analyse de

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20 essais randomisés dans laquelle le groupe de PVVIH naïves commençant le DTG avait un taux de suppression virologique à la semaine 96 significativement plus élevé par rapport au groupe traité par IPb, éfavirenz et elvitégravir potentialisé par le cobicistat (73).

Puissance, demi-vie et barrière génétique des ARV déterminent leur pardonance aux doses manquées. La tolérance pharmacocinétique du régime à base de DTG s'explique par la demi-vie d'élimination du DTG de 14 heures et sa durée d'effet inhibiteur élevée de 72 h (74). En revanche, le raltégravir, l'atazanavir boosté et le lopinavir boosté ont une demi-vie d'élimination terminale plus courte, respectivement 10-12, 8,3 et 2,4 heures, nécessitant une Adh-m élevée pour conserver la suppression virologique (75). Les INNTI ont une longue demi-vie plasmatique mais une barrière génétique relativement faible à l'émergence de résistance, ce qui explique leur faible pardonance aux IT.

Il y a plusieurs limites importantes à notre étude. L'adhésion a été contrôlée par PE, nous ne pouvons donc pas prouver que les ARV ont été ingérés. La meilleure approche est probablement de combiner plusieurs mesures (13), questionnaires d'auto-évaluation et dosage plasmatique du médicament. De plus, nous ne connaissons pas l'adhésion à l'ensemble de la trithérapie. La prise simultanée de plusieurs médicaments de la combinaison ARV est nécessaire pour une efficacité optimale et la prise sélective de médicaments peut entraîner des périodes de mono ou bithérapie associées à un échec virologique et à une résistance aux médicaments (76). Aussi, la durée de l'étude était courte et tout rebond virologique avant 6 mois est resté inaperçu. Enfin, nous avons comparé des groupes non randomisés de PVVIH avec différentes caractéristiques de base. En particulier, la répartition des PVVIH qui ont commencé le traitement étudié en initiation, remplacement ou échec était différente entre les groupes de traitement. L'utilisation d'une analyse multivariée avec ajustement sur les prédicteurs importants de la réplication virologique a probablement contribué à atténuer ce risque de biais.

L'étude a aussi des points forts. Notre grande taille d'échantillon de 399 PVVIH représente 73 017 événements d'adhésion avec divers ARV dont le DTG. La diversité des comportements d'adhésion nous a permis d'identifier des interactions significatives entre l'Adh-m et l'IT. Alors que des travaux antérieurs ont démontré que les interruptions de traitement à court terme pouvaient être prédites par la mesure de l'Adh-m (77), nos résultats suggèrent que ce ne sont pas des mesures interchangeables (78) et que leur influence diffère selon les ARV (79).

Nos résultats sont conformes aux recommandations actuelles de l'International Antiviral

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Society-USA (26) dans laquelle les INI de deuxième génération sont en première ligne. De plus, selon l'OMS, les trithérapies à base de DTG devraient limiter le risque d'émergence de résistance suite à des IT en raison de toxicités, d'une mauvaise rétention dans le soin ou de ruptures de stock de médicaments, qui existent dans les pays à ressources limitées (80).

Une adhésion élevée et constante doit rester l'objectif du traitement, car même si les trithérapies à base de DTG semblent pardonnantes, une adhésion sous-optimale au traitement (81) et les IT (82) sont associées à des niveaux plus élevés d'inflammation malgré une suppression virologique et sont associées à une morbidité cliniquement significative (83). Or le niveau d'observance des PVVIH n'est pas optimal. Une méta-analyse retrouva parmi 17 573 PVVIH en Amérique du Nord une adhésion déclarée > 80% pour seulement 55% (IC95%=49%-62%;  $I^2=98.6%$ ) et pour 77% (IC95%=68%-85%;  $I^2=98.4%$ ) parmi 12 116 PVVIH en ASS ( $p=0.001$ ) (84). Une revue de la littérature de la même équipe, retrouva les effets secondaires, la peur d'être reconnu infecté par le VIH et la complexité du traitement, comme principales barrières à l'adhésion thérapeutique dans les pays développés ; et les effets secondaires, être loin du domicile et l'accès au traitement comme principales barrières à l'adhésion thérapeutique dans les pays en voie de développement (85).

Le niveau d'adhésion et les motifs de mauvaise observance sont divers en fonction des contraintes. Peu d'études ont cherché à caractériser les patients non adhérents. Pourtant connaître ces facteurs pourrait guider la prise en charge et la prescription de molécules plus pardonnantes. Aux États-Unis, une étude a retrouvé comme facteurs corrélés à une faible adhésion, être une femme, d'origine non caucasienne, de niveau d'éducation faible, au chômage et de faibles revenus (86). Une autre étude communautaire américaine a retrouvé comme facteurs de suppression virologique, être âgé  $\geq 50$  ans (ORa=2,33; IC95%=1,70-3,21) et être un homme (ORa=1,49; IC95%=1,07-2,08) et comme facteur de non-suppression, l'origine africaine (ORa=0,46; IC95%=0,33-0,64) comparativement aux autres origines ethniques (68). Dans une étude brésilienne, l'unique FDR de bonne adhésion en analyse multivariée était la trithérapie simplifiée en prise unique, (OR=2,3; IC95%=1,2-4,4;  $p=0.01$ ) indépendamment du sexe, âge, revenus, éducation et usages de toxiques (87).

L'adhésion diminue au fil du temps, une période de « lune de miel » d'un mois après le début du traitement est retrouvée avant que le taux d'adhésion ne commence à baisser (88). Mais, il existe une différence d'effet des facteurs d'adhésion selon la phase du traitement par INNTI, initiale ou maintenance. Dans une étude réalisée au Cameroun, une non-observance précoce

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était indépendamment associée à l'échec virologique (ORa=7,2; IC95%=1,5-34,6), alors que seules les interruptions de traitement avaient un impact significatif sur l'échec virologique pendant la phase d'entretien (Ora=2,1; IC95%=1,1-4,4) (89). L'optimisation de l'observance au cours des premiers mois du traitement est donc cruciale.

Nous avons trouvé dans notre précédente étude sur la rétention dans le soin, qu'un délai court avant mise sous premier ARV et le fait même d'être sous ARV sont des facteurs de bon suivi médical (Article 1 et 2). Dans une étude suisse étudiant un programme d'amélioration de l'adhésion thérapeutique, une meilleure adhésion au traitement entraînait un meilleur suivi des PVVIH (90). Ce programme comportait l'utilisation par les PVVIH de PE, des entretiens motivationnels, des entretiens d'éducation thérapeutique avec rendu des résultats électroniques d'adhésion, en lien avec le médecin traitant pour assurer la continuité des soins et une aide sociale ou psychologique si nécessaire (91). Les ISM  $\geq$  12 mois étaient significativement plus fréquentes dans le groupe contrôle (75/311, 22,6%) par rapport au groupe interventionnel (56/451, 12,5%),  $p < 0,001$  (90).

Ainsi, il est difficile pour le moment de prédire quel sera le niveau d'adhésion de nos patients mais nous pouvons caractériser leur niveau d'adhésion thérapeutique et le risque d'IT par l'interrogatoire, un questionnaire et/ou l'utilisation de PE. Nous pouvons les aider à améliorer leur observance en fonction des obstacles rencontrés : diminuer les effets secondaires, simplifier le traitement, aider à la distribution du traitement, prendre en charge les addictions et les difficultés sociales. Encourager et éduquer les PVVIH pour obtenir la meilleure observance thérapeutique est crucial mais il est aussi important de prescrire une trithérapie adaptée au niveau d'adhésion réel de nos patients, au risque d'IT, avec pour but l'obtention d'une suppression virale durable.

### **c) Importance des caractéristiques individuelles dans la stratégie d'allègement thérapeutique**

Dans une méta-analyse sur données individuelles de quatre essais cliniques européens, nous avons trouvé un risque plus élevé d'échec virologique chez les participants ayant reçu du DTG-m comme traitement de maintenance par rapport au traitement standard (Publication n°4). Parmi les 272 participants sous DTG-m, 18 (6,6 %) étaient en échec virologique. Le taux d'incidence de l'échec virologique était estimé à 1,69/1000 p-a. Les participants sous DTG-m

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présentaient un risque augmenté d'échec virologique si le délai avant le premier ARV était  $\geq 90$  jours après le diagnostic, si le nadir des lymphocytes T CD4 était  $< 350/\text{mm}^3$ , lorsqu'un signal PCR d'ARN VIH plasmatique était détecté à l'inclusion et lorsque le taux d'ADN proviral à l'inclusion était  $\geq 2,7 \log/10^6$  cellules mononuclées du sang périphérique (PBMCs). L'efficacité du DTG-m différait entre les sous-groupes de population en fonction du nadir de CD4, du délai avant mise sous ARV et du niveau d'ADN proviral au départ.

Une méta-analyse évaluant le DTG-m trouva une proportion plus importante d'échec virologique 8,9 % (IC95%=4,7%-16,2%) à la semaine 48 (37). Dans une cohorte rétrospective française, trois échecs virologiques sont survenus parmi 61 (4,9%) participants sous DTG-m, et l'incidence de l'échec virologique était de 2,45 pour 100 p-a à S48. Ce taux plus élevé que dans notre étude, peut s'expliquer par les caractéristiques des individus inclus, les trois individus avec échec virologique avaient déjà reçu un traitement à base d'INI et un individu avait une mutation associée à la résistance à l'INI à l'inclusion (92,93). Dans une cohorte rétrospective allemande, le taux d'échec virologique était plus faible avec 1 /31 (3,2 %) individus suivis pendant 24 semaines (94). Or, il est important de souligner que la plupart des échecs virologiques de notre étude sont survenus après la semaine 24.

Les participants sous DTG-m avaient un risque 5 fois plus élevé d'échec virologique lorsque le délai avant le premier ARV était  $\geq 90$  jours après le diagnostic, un risque 12 fois plus élevé lorsque le nadir de CD4 était  $< 350/\text{mm}^3$ , un risque quatre fois plus élevé lorsqu'un signal PCR d'ARN VIH plasmatique était détecté à la mise sous DTG-m et plus de trois fois en cas de taux d'ADN proviral  $\geq 2,7 \log /10^6$  PBMCs à la mise sous DTG-m. Notre étude renforce les résultats de DOMONO en attestant de l'indépendance des FDR d'échec sous DTG-m (95).

La présence d'un signal PCR d'ARN plasmatique et le niveau d'ADN proviral sont les deux marqueurs de la taille du réservoir chez les PVVIH contrôlées (96). Le taux d'ADN proviral chez les patients sous ARV efficaces pendant  $> 6$  mois reflète principalement l'ADN du VIH-1 intégré et un taux bas est associé à un risque faible de progression de la maladie, de rebond virologique et de résistance aux médicaments (97). Le nadir de CD4 et le délai avant l'initiation des ARV ont été rapportés comme prédicteurs indépendants du niveau d'ADN proviral après une suppression virologique (98,99). Dans notre étude, il existait une association indépendante entre le taux d'ADN proviral à l'inclusion et l'échec virologique, et entre le nadir de CD4 et l'échec virologique. Ces deux facteurs étaient également décrits comme des FDR d'échec virologique sous monothérapie d'IP (100–102).

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La différence de risque la plus élevée entre DTG-m et le groupe contrôle était retrouvée quand le taux d'ADN proviral était  $\geq 2.7 \log / 10^6$  PBMCs (32%). L'hétérogénéité la plus importante fut également retrouvée dans l'analyse en sous-groupe en fonction du taux d'ADN proviral ( $I^2=80,2\%$ ). Ainsi, la taille du réservoir viral pourrait être le déterminant clé de l'échappement virologique en monothérapie. Un niveau d'ADN proviral plus élevé conduit à un risque plus élevé de réactivation de provirus hébergeant une mutation associée à la résistance aux INI. Dans l'essai EARLY-SIMPLIFIED, un seul échec virologique s'est produit et il ne répondait pas à la définition de primo-infection. La faible diversité génétique du VIH dans la primo-infection et un système immunitaire préservé peuvent expliquer les bons résultats virologiques de DTG-m en simplification précoce (103,104).

Aucun échec virologique n'a pu être expliqué par une concentration plasmatique sous-optimale de DTG. Les études précédentes n'ont pas retrouvé de concentrations plasmatiques plus faibles en cas d'échec virologique, confirmant la robustesse du DTG (31,92,105). L'hypothèse d'une différence de concentration de médicament entre le secteur plasmatique et les sites sanctuaires a été explorée dans l'essai EARLY-SIMPLIFIED (38). Tous les taux de DTG mesurés dans le LCR au départ et à la semaine 48 dépassaient l'IC 50 in vitro pour le VIH-1 de type sauvage et atteignaient des concentrations thérapeutiques dans le SNC. Diverses études évaluant la monothérapie d'IP ont identifié une adhésion sous-optimale comme facteur d'échec virologique (102,105). Mais dans notre IPDMA, aucun échec virologique n'a pu être expliqué par une adhérence suboptimale.

Près de la moitié des participants avec échec virologique ont développé une mutation associée à une résistance dans le gène de l'intégrase. Ce résultat est cohérent avec la méta-analyse précédente (37). Dans une étude de cohorte française étudiant le DTG-m, les trois échecs virologiques sous DTG-m ont eu une émergence de résistance à l'INI, expliquée par une exposition précédente aux INI et une résistance à l'INI déjà présente à l'inclusion (93). Or ce n'était pas le cas pour aucun participant de notre IPDMA. Les mutations développées sous DTG-m dans notre étude étaient majoritairement la N155H, puis on retrouvait la S147G, R263K, E138K et S230R. Le risque conféré par une mutation de novo est une résistance croisée aux autres INI disponibles ou futures. Nos résultats ont montré que la barrière génétique à la résistance du DTG est insuffisante en monothérapie.

L'autre moitié des échecs virologiques n'était pas liée à une résistance aux INI. L'équipe de DOMONO a émis l'hypothèse qu'une réactivation stochastique d'une cellule unique



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hébergeant un provirus avec un INSTI-RAM ou des mutations dans la région 3'-PPT pourraient expliquer une partie des échecs virologiques sous DTG-m (106). La grande variation du temps avant échec virologique observée dans notre IPDMA joue en faveur de cette hypothèse.

Les événements indésirables graves et les événements liés aux traitements étaient rares et moins fréquents chez les participants du groupe DTG-m comparé au groupe témoin. Aucun participant sous DTG-m n'a interrompu le traitement en raison d'effets indésirables. L'effet neuropsychiatrique était l'effet indésirable le plus fréquemment rapporté, ce qui est cohérent avec les études précédentes évaluant le DTG-m (93,107).

Notre étude présente plusieurs forces. Tous les essais cliniques randomisés publiés évaluant le DTG-m ont été inclus, ce qui a permis une importante base de données. Une IPDMA a pu être réalisée grâce à une méthodologie similaire entre les essais. Tous étaient des essais multicentriques ouverts de non-infériorité. Grâce à la réalisation d'une IPDMA, nous avons pu utiliser un critère de jugement principal homogène. Même si l'incidence d'échec virologique était faible, nous avons pu analyser et publier le premier modèle multivarié de FDR d'échec virologique sous DTG-m grâce à cette collaboration européenne.

La première limite de notre étude est l'absence d'échec virologique dans le groupe contrôle qui n'a pas permis un modèle de Cox pour l'analyse de l'hétérogénéité. Ensuite, seules des études européennes sont incluses dans l'IPDMA ce qui interroge sur la généralisation des résultats. Nous avons un manque de données d'ADN proviral à la mise sous monothérapie et surtout un manque quasi-total de mesures d'ADN proviral au moment de l'échec virologique, ce qui n'a pas permis d'analyser cette variable. Dans les études observationnelles, le taux d'ADN proviral ne change pas de manière significative entre le départ et à la semaine 48 de DTG-m (84,99). Cela suggère que le réservoir latent du VIH-1 ne se reconstitue pas sous DTG-m. Enfin, concernant l'innocuité du DTG, nous ne donnons pas de données sur le poids au cours du suivi ou sur l'évolution des tissus adipeux viscéraux ou sous-cutanés, effet secondaire connu du DTG (32,108–110).

La dernière mise à jour des recommandations de l'EACS recommande la bithérapie à base de DTG comme thérapie d'entretien (26). Pour certaines PVVIH présentant un virus résistant à plusieurs classes thérapeutiques ou des conditions médicales réduisant les possibilités de traitement, la monothérapie fonctionnelle est envisagée. Notre étude a montré que la DTG-m n'entraînait pas d'échec virologique après 48 semaines chez les PVVIH avec un nadir élevé de

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CD4 et un taux faible d'ADN proviral. La robustesse du DTG a déjà été démontrée en cas de bi et monothérapie fonctionnelle. Dans un essai clinique randomisé évaluant la trithérapie à base de DTG, il n'y avait pas de différence significative de succès virologique parmi les participants sous DTG, emtricitabine et tenofovir alafenamide avec ou sans résistance connue aux INNTI, 97% versus 89% et 94% versus 91% avec présence d'une M184V/I (109). L'étude SWORD retrouva une efficacité virologique de la bithérapie DTG-rilpivirine sans risque augmenté de survenue d'une résistance aux INI (40). Parmi les 11 participants en échec virologique, six ont développé une résistance à la rilpivirine et aucun au DTG. L'étude TANGO évaluant la bithérapie DTG-lamivudine, retrouva une absence d'échec virologique parmi quatre participants présentant une M184V/I mutation (43). Dans une étude rétrospective récente, parmi 19 monothérapie fonctionnelle de DTG et 20 bithérapie fonctionnelle incluant du DTG, une CV persistante > 50cp/mL a été observée chez respectivement 2 (11%) et 5 (25%) participants (111). Les auteurs ont expliqué l'échec virologique en raison d'une adhésion sous-optimale.

Dans les pays en voie de développement, plusieurs études ont retrouvé un succès virologique parmi les PVVIH traitées par DTG malgré un taux élevé de résistance aux INNTI et de mutation M184V/I (112–115). Dans l'étude DAWNING, seulement 16% (51/312) des participants sous trithérapie à base de DTG étaient en échec virologique alors que 84% (261/312) présentaient une mutation M184V/I (113). L'OMS recommande donc un traitement à base de DTG en deuxième ligne de traitement malgré le risque important de mono et bithérapie fonctionnelle (80).

## VI. CONCLUSION

Nous avons retrouvé un taux d'incidence différent et des facteurs associés à l'ISM différents entre les cohortes de PVVIH suivies à Caen et à Bichat. Ceci reflète l'hétérogénéité des populations en fonction de la zone géographique. Nos résultats pourraient aider les cliniciens à identifier les patients qui sont à risque d'interrompre leur suivi dès le début de leur prise en charge. À l'hôpital Bichat, il s'agit des personnes immunodéprimées, des personnes qui ne sont pas suivies en dehors de l'hôpital, des personnes nées en France et des personnes qui habitent dans le 18<sup>e</sup> arrondissement de Paris. Dans le centre de Caen, les personnes-cibles sont les personnes prises en charge tardivement après le diagnostic de VIH, les personnes co-infectées VIH-VHC, les personnes sans adresse disponible dans le dossier, les personnes nées en ASS et les personnes de moins de 30 ans. Les interventions communes aux deux centres seraient la prise en charge précoce du patient après son diagnostic et la mise en route rapide d'un traitement ARV.

Concernant l'adhésion au traitement, nos résultats suggèrent que les PVVIH avec un niveau d'adhésion faible à modéré ( $\leq 95\%$ ) traitées avec une combinaison à base de DTG présentent un risque plus faible de répllication virale que celles traitées avec des ARV plus anciens. Bien que de nombreux facteurs non évalués dans ce travail devraient influencer le choix du traitement ARV, notamment la tolérance, le nombre de comprimés, la préférence des patients, le risque d'interaction médicamenteuse et les coûts, nous recommandons d'utiliser des schémas thérapeutiques à base de DTG pour les PVVIH qui luttent pour atteindre un niveau d'observance élevé ou celles à risque d'IT. Nous avons étudié la trithérapie à base de DTG, par conséquent, nos résultats ne doivent pas être généralisés aux bithérapies à base de DTG (avec rilpivirine ou lamivudine) ou à la trithérapie à base de bictégravir. Des recherches plus poussées sur la pardonnance des INI de seconde génération sont justifiées.

Enfin, notre IPDMA a illustré la nécessité d'explorer le niveau d'ADN proviral avant la simplification du traitement par DTG-m et d'être particulièrement prudent chez les PVVIH mis sous premier ARV  $\geq 90$  jours après le diagnostic du VIH, présentant un nadir de CD4  $< 350/\text{mm}^3$ , un signal PCR positif d'ARN plasmatique et/ou un taux d'ADN proviral  $\geq 2,7 \log / 10^6$  PBMCs. Le problème majeur était le développement de mutations de résistance aux INI en cas d'échec virologique, qui réduit les options de traitement futures. La quantification de l'ARN

## VI. Conclusion

et de l'ADN proviral dans le sang et la connaissance de l'histoire de la maladie devraient aider les médecins à sélectionner les candidats pour une monothérapie de DTG en traitement de maintenance. Un nouvel essai clinique évaluant le DTG-m incluant des PVVIH avec une bonne adhérence, sans historique d'échec virologique, ni de résistance, avec un nadir de CD4 > 350 /mm<sup>3</sup>, ayant bénéficié d'une prise en charge thérapeutique précoce après le diagnostic de l'infection, présentant une CV indétectable et un taux d'ADN proviral < 2,7 log / 10<sup>6</sup> PBMCs pourraient confirmer nos résultats.

Le contexte socio-démographique, l'histoire de l'infection VIH, le statut immuno-virologique antérieur et actuel associés à la connaissance du niveau d'observance des PVVIH permettent de guider le choix thérapeutique et les efforts nécessaires pour améliorer le succès virologique et l'adhésion aux soins. Ainsi, la prise en charge des PVVIH, renforcée ou allégée, doit être adaptée aux caractéristiques individuelles.

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## **Importance des caractéristiques individuelles dans la rétention dans le soin, l'observance et l'allègement thérapeutique des personnes vivant avec le VIH**

**Introduction :** Pour de nombreuses personnes vivant avec le VIH (PVVIH), un allègement thérapeutique est envisageable, tandis que pour d'autres un traitement pardonnant les doses manquées est nécessaire, avec parfois une prise en charge renforcée pour éviter une interruption de soins médicaux (ISM). Nos objectifs étaient de déterminer l'incidence et les facteurs de risque (FDR) d'ISM dans deux cohortes de PVVIH ; d'étudier la pardonnance de la trithérapie à base de dolutégravir (DTG) par rapport aux régimes antirétroviraux (ARV) plus anciens ; de déterminer les FDR d'échec virologique sous DTG en monothérapie (DTG-m) et d'explorer l'hétérogénéité du risque comparé à une trithérapie classique, en fonction des FDR identifiés.

**Méthodes :** Nous avons estimé l'incidence d'ISM chez 4 796 PVVIH suivies au centre hospitalier universitaire (CHU) Bichat à Paris et chez 989 PVVIH suivies au CHU de Caen, entre janvier 2010 et mai 2016. Les patients furent considérés en ISM s'ils ne recevaient aucuns soins médicaux pendant 18 mois ou plus. Nous avons constitué une cohorte prospective multicentrique des modèles d'adhésion aux ARV. L'adhésion moyenne (Adh-m) et la durée maximale d'interruption de traitement (ITmax) ont été mesurées prospectivement sur 6 mois à l'aide de piluliers électroniques. Nous avons réalisé une méta-analyse sur données individuelles des essais cliniques évaluant le DTG-m. La population d'étude était constituée de PVVIH contrôlées sur le plan virologique depuis plus de 6 mois, et suivies pendant 48 semaines. L'échec virologique était défini par deux charges virales > 50 copies/mL avant la semaine 48.

**Résultats :** Le premier travail retrouva un taux d'incidence d'ISM dans la cohorte de Bichat à 2,5 pour 100 personnes-années (p-a ; intervalle de confiance à 95% [IC95%]=2,3-2,7) et dans la cohorte de Caen à 3,0 pour 100 p-a (IC95%=2,6-3,5). Les FDR indépendamment associés à l'ISM similaires entre les cohortes de Bichat et Caen étaient un délai avant la prise en charge du VIH > 6 mois, et l'absence de traitement ARV. Dans la cohorte de Bichat, ne pas avoir de médecin traitant et avoir un taux de CD4  $\leq$  350/mm<sup>3</sup> au cours du suivi étaient associés à un plus grand risque d'ISM. Dans la cohorte de Caen, les FDR étaient : ne pas avoir renseigné d'adresse postale et être co-infecté avec le virus de l'hépatite C. Être âgé de plus de 45 ans était associé à un moindre risque d'ISM vs.  $\leq$  30 ans. Enfin, être né en Afrique sub-saharienne était un FDR d'ISM à Caen vs. né en France, et un facteur protecteur à Bichat.

Le deuxième travail regroupa 399 PVVIH avec différents ARV en 3<sup>e</sup> agent : DTG (n=102), raltégravir (n=90), inhibiteur de protéase boosté (IPb ; n=107) et inhibiteur non nucléosidique de la transcriptase inverse (INNTI ; n=100). Dans le groupe DTG, l'effet des mesures d'adhésion sur la répllication virale (R<sup>2</sup>) était marginal (+2 %). Adh-m, ITmax et Adh-m x ITmax augmentaient le R<sup>2</sup> de 54 % et 40 % dans les groupes raltégravir et IPb, respectivement. ITmax augmentait le R<sup>2</sup> de 36 % dans le groupe INNTI. Comparé au groupe DTG, le risque d'échec virologique était significativement augmenté pour les groupes raltégravir, INNTI et IPb chez les PVVIH avec une Adh-m  $\leq$  95 %.

Le troisième travail inclut 416 PVVIH, 101 de l'essai suisse EARLY-SIMPLIFIED, 95 de l'essai hollandais DOMONO, 62 de l'essai espagnol DOLAM et 158 de l'essai français MONCAY. Seize échecs furent retrouvés, tous dans le groupe sous DTG-m. Parmi 272 PVVIH traitées par DTG-m, les facteurs indépendants d'échec virologique étaient le nadir de CD4 < 350 cellules/mm<sup>3</sup>; un délai entre le diagnostic de l'infection VIH et le premier ARV > 90 jours ; un taux d'ADN proviral à l'inclusion  $\geq$  2,7log/10<sup>6</sup> PBMCs et la présence d'un signal PCR positif d'ARN VIH plasmatique. Nous avons trouvé que l'échec virologique était expliqué en majeure partie par le niveau d'ADN proviral à l'inclusion (I<sup>2</sup>=80,2%) avec une différence de risque de 32% entre le groupe DTG-m et le groupe contrôle, parmi les PVVIH avec un taux d'ADN proviral  $\geq$  2,7 log/10<sup>6</sup> PBMCs.

**Conclusion :** Le contexte socio-démographique, l'histoire de l'infection VIH, le statut immuno-virologique antérieur et actuel associés à la connaissance du niveau d'observance des PVVIH permettraient de guider le choix thérapeutique et les efforts nécessaires pour améliorer le succès virologique. Ainsi, la prise en charge des PVVIH, renforcée ou allégée, devrait être adaptée aux caractéristiques individuelles.

**Mots-clefs :** interruption de soins médicaux, adhésion au traitement, monothérapie, cohorte hospitalière, VIH