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Efficacy of raltegravir-based regimens for antiretroviral treatment of people with HIV and tuberculosis in low - and middle-income countries : insight from clinical trials

Nathalie De Castro

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THÈSE PRÉSENTÉE

POUR OBTENIR LE GRADE DE

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L'UNIVERSITÉ DE BORDEAUX

ÉCOLE DOCTORALE SOCIÉTÉS, POLITIQUE, SANTÉ PUBLIQUE

Santé Publique, Épidémiologie

Par Nathalie De Castro

**EFFICACITÉ D'UNE COMBINAISON ANTIRETROVIRALE
COMPRENANT LE RALTEGRAVIR POUR LE TRAITEMENT DES
PERSONNES VIVANT AVEC LE VIH ET TRAITÉES POUR UNE
TUBERCULOSE : MISE EN PERSPECTIVE À PARTIR DE DONNÉES
D'ESSAIS CLINIQUES**

**EFFICACY OF RALTEGRAVIR-BASED REGIMENS FOR
ANTIRETROVIRAL TREATMENT OF PEOPLE WITH HIV AND
TUBERCULOSIS IN LOW- AND MIDDLE-INCOME COUNTRIES:
INSIGHT FROM CLINICAL TRIALS**

Soutenue le 14 décembre 2022

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Titre : Efficacité d'une combinaison antirétrovirale comprenant le raltegravir pour le traitement des personnes vivant avec le VIH et traitées pour une tuberculose : mise en perspective à partir de données d'essais cliniques.

Chez les personnes vivant avec le VIH (PVVIH) et la tuberculose, la gestion du traitement antirétroviral (ARV) est complexe en raison des interactions médicamenteuses avec la rifampicine, l'un des principaux antituberculeux. L'objectif de cette thèse était d'évaluer si le raltegravir, un inhibiteur d'intégrase (INI), pourrait être proposé dans cette situation. Cette thèse s'appuie principalement sur les résultats de l'essai ANRS 12300 Reflate TB2. Il s'agissait d'un essai de phase III, en ouvert, randomisé, de non-infériorité, mené entre 2015 et 2018 au Brésil, en Côte d'Ivoire, en France, au Mozambique et au Vietnam. Au total, 460 PVVIH traitées pour tuberculose et naïves de traitement antirétroviral ont reçu du raltegravir 400 mg deux fois par jour, ou de l'éfavirenz, tous deux en association avec le ténofovir et la lamivudine. À l'inclusion, la médiane de lymphocytes T CD4+ était de 103/mm³ et la médiane de charge virale VIH-1 de 5,5 Log₁₀ copies/mL. À la semaine 48, 140 (61 %) participants sous raltegravir et 150 (66 %) participants sous éfavirenz avaient un ARN VIH-1 < 50 copies/mL ; différence : -5,2 % ; IC à 95 % - 14,0 à +3,6 ; marge de non-infériorité 12 %) ; la non-infériorité n'a donc pas été démontrée. La proportion de patients avec une adhésion au traitement ARV <95% était de 43 % sous raltegravir et de 27 % sous éfavirenz (p < 0,0001). Les taux d'événements indésirables étaient similaires dans les deux bras. Pour mieux comprendre les déterminants du succès virologique et de l'adhésion aux ARV, nous avons réalisé une analyse secondaire chez 444 participants avec des données d'adhésion disponibles. Sur 48 semaines, 290/444 (65 %) participants avaient une observance ≥ 95 %. Le sexe féminin, le niveau d'ARN VIH-1 < 100.000 copies/mL à l'initiation des ARV et l'observance ≥ 95 % étaient indépendamment associés au succès virologique. Le nombre de comprimés ARV était le seul facteur associé une observance ≥ 95 %. Nous avons fusionné les données de l'essai ANRS 12180 Reflate TB (2009-2011) avec les données de l'essai ANRS 12300 Reflate TB2 afin d'analyser les différences entre pays. L'essai ANRS 12180 Reflate TB était un essai randomisé de phase II, évaluant deux doses de raltegravir et l'éfavirenz chez des PVVIH majoritairement brésiliennes avec une tuberculose. Le taux de succès virologique à la semaine 48 dans le groupe raltegravir 400 était de 76 %, similaire à celui des groupes éfavirenz ou raltegravir 800. Nous avons inclus 550 participants dans l'analyse poolée (97 de l'essai de phase II et 453 de l'essai de phase III):140 venaient du Brésil, 170 de Côte d'Ivoire, 129 du Mozambique et 111 du Vietnam. Les médianes de charge virale à l'inclusion et les taux de succès virologique étaient respectivement 4,9, 5,6, 5,3 et 5,6 Log₁₀ copies/mL et 105/140 (75,0 %), 99/170 (58,2 %), 84/129 (65,1 %) et 74/111 (66,7 %) au Brésil, en Côte d'Ivoire, au Mozambique et au Vietnam (p<0,0001 et p=0,0217). Une charge virale < 100,000 copies était le seul facteur indépendamment associé au succès virologique. Cette analyse a également montré la non-infériorité du raltegravir par rapport à l'éfavirenz avec 177/277 (63,9%) patients sous raltegravir et 185/273 (67,8%) sous éfavirenz en succès virologique à la semaine 48 (différence -3,9% (-11,8% ; 4,1 %)). Cette thèse montre que le raltegravir pourrait être utilisé pour traiter les PVVIH ayant une tuberculose. Pour les niveaux de charge virale les plus élevés, l'efficacité virologique était inférieure à ce qui est attendu avec le raltegravir et l'éfavirenz, notamment lorsque l'observance était suboptimale. L'analyse des données des programmes de lutte contre le VIH et la tuberculose dans chaque pays est essentielle, en particulier avec le déploiement récent dans les pays à revenu faible et intermédiaire d'un autre INI, le dolutegravir.

Mots clés : VIH, tuberculose, raltegravir, traitement antirétroviral, pays du Sud

Title: Efficacy of raltegravir-based regimens for antiretroviral treatment of people with HIV and tuberculosis in low- and middle-income countries: insight from clinical trials.

In people with HIV (PWH) and tuberculosis, management of antiretroviral therapy (ART) is complex due to drug-drug interactions between antiretrovirals and rifampicin, one of the main tuberculosis drugs. The objective of this thesis was to evaluate if the integrase strand transfer inhibitor (INSTI) raltegravir could be proposed for ART in PWH treated concomitantly for tuberculosis. The thesis work is based mostly on the ANRS 12300 Reflate TB2 trial. It was an open-label, randomised, non-inferiority phase III trial, conducted between 2015 and 2018 in Côte d'Ivoire, Brazil, France, Mozambique and Vietnam. Overall, 460 ART-naïve HIV-1-infected adults with tuberculosis were randomized to receive either raltegravir 400 mg twice daily or efavirenz 600 mg once daily, both in combination with tenofovir and lamivudine. Patients' median baseline CD4⁺ cell count was 103/mm³ and median plasma HIV-1 RNA was 5.5 Log₁₀ copies/mL. At week 48, 140 (61%) participants on raltegravir- and 150 (66%) on efavirenz-based ART achieved virologic success (HIV-1 RNA <50 copies/mL; difference: -5.2%; 95% CI -14.0 to +3.6; non-inferiority margin 12%), non-inferiority was not shown. The proportion of participants with sub-optimal adherence (pill count adherence ratio <95%) was 43% on raltegravir and 27% on efavirenz (p<0.0001). Rates of adverse events were similar in both arms. To better understand determinants of virologic success and adherence, we conducted a secondary analysis in 444 participants with adherence data available. Over 48 weeks, 290/444 (65%) participants had a pill count adherence ratio ≥95%. Female sex, baseline HIV-1 RNA levels <100,000 copies/mL and pill count adherence ratio ≥95% were independently associated with virologic success. Antiretroviral pill burden was the only factor associated with pill count adherence ratio ≥95%. We pooled data from the ANRS 12180 Reflate TB phase II trial (2009-2011) with data from the ANRS 12300 Reflate TB2 trial to further explore differences between countries participating to both trials. ANRS 12180 Reflate TB trial was a multicentre, open-label, randomized, phase II trial, where 153 ART-naïve PWH with tuberculosis from Brazil or France were randomised to receive raltegravir (400 or 800 mg twice daily) or efavirenz (600 mg once daily), in combination with tenofovir and lamivudine. Virologic suppression at week 48 with raltegravir 400 mg twice daily was 76%, which was similar to efavirenz or raltegravir 800 twice daily. We included 550 participants (97 from the phase II and 453 from the phase III trial) in the pooled analysis: 140 from Brazil, 170 from Côte d'Ivoire, 129 from Mozambique and 111 from Vietnam. Median baseline HIV-1 RNA and virologic success rates were 4.9, 5.6, 5.3, and 5.6 Log₁₀ copies/mL and 105/140 (75.0%), 99/170 (58.2%), 84/129 (65.1%) and 74/111 (66.7%) in Brazil, Côte d'Ivoire, Mozambique and Vietnam, respectively (p<0.0001 and p=0.0217). Lower baseline HIV-1 RNA was the only factor independently associated with virologic success. This analysis also showed the non-inferiority of raltegravir compared to efavirenz at week 48 with 177/277 (63.9 %) patients on raltegravir and 185/273 (67.8%) on efavirenz achieved virologic success (difference -3.9% (-11.8%; 4.1%)). This thesis shows that raltegravir-based ART could be used to treat PWH with tuberculosis. However, in participants with high HIV RNA, virologic efficacy rates were lower than expected both with raltegravir and efavirenz, especially when adherence was suboptimal. Further analyzing data from national HIV and tuberculosis programs on virologic success rates in PWH with tuberculosis is therefore key, especially with the recent roll out of the second generation INSTI dolutegravir in low- and middle-income countries.

Keywords: HIV, tuberculosis, raltégravir, antiretroviral treatment, LMICs

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List of abbreviations/glossary

1HP: one month treatment with daily rifapentine and isoniazid

3HP: three months treatment with weekly rifapentine and isoniazid

3HR: four months treatment with daily isoniazid and rifampicin

4R: four months treatment with daily rifampicin

AE: Adverse Events

AFB: Acid-Fast Bacilli

ACTG: AIDS Clinical Trials Group

AUC: Area Under the Curve

ART: Antiretroviral Therapy

AZT: zidovudine

BCG: Bacille Calmette et Guérin

BPaL: Bedaquiline, Pretomanid, Linezolid

BPaLM: Bedaquiline, Pretomanid, Linezolid, Moxifloxacin

BpaMZ: Bedaquiline, Pretomanid, Moxifloxacin and pyrazinamide

CD4 counts: CD4 + T-cell counts

cART: combined ART

DOT: Directed Observed Therapy

C_{12h}: Concentration 12 hours after drug intake (or trough concentration)

C_{max}: maximum concentration after drug intake (or peak concentration)

COVID-19: COronaVirus Disease 2019

CSF: Cerebro-Spinal Fluid

DST: Drug Susceptibility Testing

DTG: dolutegravir

EFV: efavirenz

FTC: emtricitabine

GMR: Geometric Mean Ratio

HIV: Human Immunodeficiency Virus

IC95: 95% inhibitory concentration

IDMC: Independent Data Monitoring Committee

IGRA: Interferon gamma releasing assay

IFN: Interferon

INSTI: Integrase Strand Transfer Inhibitor

IRIS: Immune Restoration Inflammatory Syndrome

IPT: Isoniazid Preventive Therapy

LTBI: Latent Tuberculosis Infection

MDR/RR-TB: Multidrug-Resistant/Rifampicin Resistant-TB

MIC: Minimum Inhibitory Concentration

MTBC: *Mycobacterium Tuberculosis* Complex

NAAT: Nucleic Acid Amplification Tests

NRTI: Nucleoside Reverse Transcriptase Inhibitor

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor

PI/r: Protease Inhibitor boosted with Ritonavir

PK: Pharmacokinetic

PPD: Purified Protein Derivative

PWH: People With HIV

RAL: raltegravir

SoC: Standard Of Care

TAF: Tenofovir Alafenamide

TB: Tuberculosis

TDF: Tenofovir Disoproxil Fumarate

TDM: Therapeutic Drug Monitoring

T_{max}: Time to maximum concentration or peak concentration

TNF: Tumour Necrosis Factor

TPT: Tuberculosis Preventive Treatment

TST: Tuberculin Skin Test

WHO: World Health Organization

XDR-TB: eXtensively drug-resistant tuberculosis

Résumé substantiel

Introduction, traitement antirétroviral chez les personnes vivant avec le VIH traitées pour une tuberculose

L'infection par le virus de l'immunodéficience humaine (VIH) et la tuberculose (TB) sont deux pandémies qui ont la même répartition géographique dans de nombreuses régions du monde, notamment en Afrique subsaharienne, en Asie ou en Amérique du Sud. Les enjeux de la lutte contre ces deux épidémies concomitantes sont nombreux. Le traitement des deux infections nécessite la prise de nombreux comprimés, il existe des interactions médicamenteuses entre le traitement antituberculeux et le traitement antirétroviral (TARV) ainsi que des toxicités communes dont la gestion est difficile.

Les bénéfices du TARV en termes de morbidité et de mortalité, ainsi que sur la prévention de la transmission du VIH ont été largement démontrés au cours des 20 dernières années. Chez toutes les personnes vivant avec le VIH (PVVIH) atteintes de tuberculose, il est actuellement recommandé de commencer le TARV dans les deux semaines suivant le traitement antituberculeux, quel que soit le taux de CD4, à l'exception de la méningite tuberculeuse. Dans cette situation, le TARV (la « trithérapie ») doit débuter quatre semaines après le début du traitement antituberculeux. La rifampicine active la transcription de gènes impliqués dans le métabolisme et le transport de nombreux médicaments et induit le cytochrome P 450 (CYP), l'UDP-glucuronosyltransférase (UGT)1A1 et le transporteur d'efflux P-glycoprotéine. Ces voies métaboliques sont impliquées dans le métabolisme de la plupart des médicaments antirétroviraux, en particulier le CYP3A4 et le CYP2B6. Les CYP3A4 et CYP2B6 hépatiques sont des voies métaboliques majeures pour les inhibiteurs de protéase (IP), les inhibiteurs non-nucléosidiques de la reverse transcriptase (INNTI) mais aussi les inhibiteurs de l'intégrase (INI), entraînant donc une baisse importante des taux plasmatiques de la plupart des molécules utilisées comme troisième agent dans les combinaisons du TARV. L'interaction entre la rifampicine et l'efavirenz, un INNTI, entraîne une réduction modeste des taux d'efavirenz, sans conséquences sur l'efficacité virologique, comme l'ont démontré plusieurs études pharmacocinétiques ou essais randomisés évaluant un TARV comprenant l'efavirenz. L'efavirenz est donc devenu le traitement de choix pour le traitement des PVVIH atteintes de tuberculose. Depuis 2018, un INI, le dolutégravir, est disponible dans les programmes de lutte contre le VIH dans les pays à revenus faibles ou intermédiaires. Avant cette date, conformément à la recommandation de l'OMS, l'efavirenz était le traitement de première ligne et les alternatives pour le traitement de deuxième ligne étaient les IP boostés par le ritonavir.

Les schémas thérapeutiques actuels pour les PVVIH naïves de TARV qui ne reçoivent pas de traitement antituberculeux concomitant consistent en l'association de deux inhibiteurs nucléosidiques de la reverse transcriptase (INTI) avec un troisième agent parmi l'une des classes suivantes : INI, INNTI ou IP boosté (par cobicistat ou ritonavir). Les options préférentielles sont le ténofovir disoproxil fumarate (TDF) ou le ténofovir alafenamide (TAF) en association avec la lamivudine (3TC) ou l'emtricitabine (FTC). Les

INI de deuxième génération sont le troisième agent recommandé préférentiellement dans la plupart des recommandations internationales. Le dolutégravir est un INI de deuxième génération qui s'est avéré non inférieur à l'éfavirenz, avec un meilleur profil de tolérance. Il est également non inférieur au raltégravir, avec l'avantage d'une prise quotidienne unique. Le dolutégravir présente plusieurs autres avantages par rapport aux INI de première génération. Il a une barrière génétique élevée pour la résistance avec une émergence de résistance survenant très rarement. En comparaison du raltégravir, il est administré une fois par jour et a été développé en co-formulation avec différentes combinaisons d'INTI dans des schémas thérapeutiques à un seul comprimé. De plus, il est moins sujet aux interactions médicamenteuses. Toutes ces raisons ont incité l'OMS à recommander des schémas thérapeutiques comprenant dolutégravir pour toutes les PVVIH depuis 2018, y compris lors de la co-administration d'un traitement antituberculeux avec nécessité de doubler la dose de dolutégravir dans ce contexte. Après ces recommandations, les programmes nationaux ont organisé leur transition des combinaisons avec éfavirenz vers des combinaisons comprenant le dolutégravir.

La recherche d'alternatives à l'éfavirenz dans le contexte de la co-infection tuberculeuse a été intense, mais à ce jour, aucun traitement n'a été plus efficace que l'éfavirenz. Le raltégravir est l'un des INI de première génération et a été la première molécule de cette famille à avoir été développée. Il est métabolisé par la glucuronidation médiée par l'UGT1A1 et n'est pas métabolisé via les cytochromes hépatiques. Cependant, la rifampicine est également un inducteur de l'UGT1A1 et le raltégravir a une interaction pharmacocinétique significative avec la rifampicine. Le doublement de la dose de raltégravir compense l'effet de la rifampicine sur l'exposition au raltégravir mais ne compense pas la réduction des concentrations minimales qui restent inférieures de 53 % aux concentrations habituelles. Ces résultats ont conduit à recommander de doubler la dose et d'utiliser le raltégravir à la posologie de 800 mg deux fois par jour en association avec la rifampicine. Cependant, il n'existait pas de données cliniques pour étayer cette recommandation et l'innocuité de fortes doses de raltégravir chez les patients recevant un traitement antituberculeux n'était pas connue.

Les données pharmacocinétiques suggèrent qu'une réduction des doses de raltégravir en présence de rifampicine pourrait avoir peu d'impact sur l'efficacité virologique du raltégravir lorsqu'il est utilisé en association avec le ténofovir et la lamivudine. Ceci a justifié l'évaluation du raltégravir à dose standard ou double dose pour le traitement des PVVIH traitées par rifampicine. L'essai ANRS 12180 Replate TB était un essai multicentrique, ouvert, randomisé, de phase II avec 51 patients par bras, mené au Brésil et en France. Des PVVIH naïves de traitement antirétroviral ont été randomisées pour recevoir du raltégravir (400 ou 800 mg deux fois par jour) ou de l'éfavirenz (600 mg une fois par jour), en association avec le ténofovir et la lamivudine (300 mg une fois par jour), après le début d'un traitement antituberculeux comprenant la rifampicine. Après la fin du traitement antituberculeux, la dose de raltégravir a été réduite à 400 mg deux fois par jour dans le bras 800 mg deux fois par jour. Dans cet essai de phase II, à la semaine 24, les taux de succès virologique (ARN VIH < 50 copies/mL) étaient de 78 %, 76 % et 63 %

dans les bras raltégravir 800, raltégravir 400 et éfavirenz, respectivement. À la semaine 48, les taux de succès étaient de 63 %, 76 % et 67 % dans les bras raltégravir 800, raltégravir 400 et éfavirenz, respectivement avec un nombre similaire d'échecs virologiques. Ces résultats devaient être confirmés dans un essai de phase III, avec un plus grand nombre de patients afin de déterminer si le raltégravir serait une alternative appropriée à l'éfavirenz et de modifier les recommandations thérapeutiques.

L'essai Reflate TB 2 était un essai de phase III comparant l'efficacité du raltégravir 400 mg deux fois par jour à celle de l'éfavirenz 600 mg une fois par jour, tous deux associés à la même combinaison d'INTI (tenofovir + lamivudine). Le critère de jugement principal était le succès virologique à la semaine 48, défini par un ARN VIH-1 < 50 copies/mL. Il s'agissait d'un des rares essais de phase III évaluant le raltégravir dans des pays à ressources limitées chez des patients naïfs de TARV et les résultats fourniraient des informations très utiles dans le contexte du déploiement de l'utilisation des INI.

L'essai Reflate TB 2 a été le premier grand essai randomisé international de phase III évaluant un régime de TARV à base d'inhibiteurs de l'intégrase dans le contexte de la co-infection VIH/TB.

L'objectif de ma thèse était d'évaluer si le raltégravir pourrait être proposé pour le traitement de l'infection par le VIH chez les personnes traitées pour tuberculose. L'hypothèse était que le raltégravir utilisé à la dose standard de 400 mg deux fois par jour pourrait être utilisé pour traiter des PVVIH naïves de TARV et atteintes de tuberculose. Dans la première partie de cette thèse, je présente un état de l'art de la tuberculose et une revue des principaux enjeux de la prise en charge concomitante de l'infection par le VIH et de la tuberculose. Je présente ensuite les résultats des trois études menées dans le cadre de ma thèse. Premièrement, les résultats de l'essai ANRS 12 300 Reflate TB 2 consistant en l'évaluation de la non-infériorité du raltégravir en comparaison de l'éfavirenz. La deuxième étude a analysé les facteurs associés au succès virologique et à l'adhésion au TARV chez les PVVIH traitées simultanément pour TB. La troisième étude a évalué les différences de taux de succès virologique entre les pays qui ont participé aux essais de phase II Reflate TB et de phase III Reflate TB 2. Nous avions initialement prévu d'évaluer l'efficacité virologique des schémas thérapeutiques comprenant raltégravir, dolutégravir ou éfavirenz chez les PVVIH traitées pour la tuberculose dans le cadre des programmes nationaux brésiliens de lutte contre le VIH et la tuberculose afin d'explorer comment les résultats des essais cliniques Reflate TB et Reflate TB2 peuvent être mis en perspective avec les données de vraie vie. En raison de la pandémie de COVID-19, ce projet a été retardé mais l'analyse devrait commencer avant la fin de 2022. Enfin, je discute de la façon dont cette thèse questionne les directives actuelles de TARV chez les PVVIH traitées pour la tuberculose et des perspectives futures.

Traitement antirétroviral comprenant raltégravir ou éfavirenz pour le traitement de personnes vivant avec le VIH et traitées pour tuberculose : résultats d'un essai ouvert, randomisé, de non-infériorité, de phase III.

Introduction :

Chez les personnes vivant avec le VIH (PVVIH) traitées pour tuberculose, les options de traitement antirétroviral sont limitées en raison des interactions médicamenteuses avec la rifampicine. Un essai de phase II a montré que le raltégravir 400 mg deux fois par jour ou l'éfavirenz 600 mg une fois par jour pourraient avoir une efficacité virologique similaire chez les patients sous rifampicine. Nous avons mené un essai de phase II pour confirmer ces résultats.

Méthodes :

ANRS 12300 Replate TB2 était un essai ouvert, randomisé, de non-infériorité mené en Côte d'Ivoire, au Brésil, en France, au Mozambique et au Vietnam. Des PVVIH adultes, en cours de traitement pour tuberculose et naïves de traitement antirétroviral (TARV) ont été randomisées pour recevoir soit du raltégravir 400 mg deux fois par jour, soit de l'éfavirenz 600 mg une fois par jour, tous deux en association avec le ténofovir et la lamivudine. Le critère d'évaluation principal était le succès virologique à la semaine 48 (ARN VIH-1 plasmatique < 50 copies/mL, algorithme snapshot de la FDA). La marge de non-infériorité était de 12 %. (Numéro d'enregistrement de l'essai : NCT02273765)

Résultats :

Au total, 230 patients ont été randomisés dans chaque bras. A l'inclusion, la médiane des CD4 était de 103/mm³ et la médiane de l'ARN VIH-1 plasmatique de 5,5 Log₁₀ copies/mL. La tuberculose a été confirmée bactériologiquement chez 310 (68 %) participants. À la semaine 48, 140 (61 %) participants sous raltegravir et 150 (66 %) sous éfavirenz étaient en succès virologique (différence : -5,2 % ; IC à 95 % -14,0 à +3,6 ; non-infériorité non démontrée). La proportion de patients avec une adhésion au traitement < 95 % était de 43 % sous raltégravir et de 27 % sous éfavirenz (p < 0,0001). La fréquence des événements indésirables étaient similaires dans les deux bras.

Interprétation :

Chez les PVVIH sous rifampicine, la non-infériorité du raltégravir par rapport à l'éfavirenz n'a pas été démontrée. L'adhésion au TARV était moins bonne dans le bras raltégravir. Le raltégravir était bien toléré et reste une alternative chez les patients qui ne peuvent pas recevoir l'efavirenz.

Facteurs associés au succès virologique et à l'adhésion au traitement antirétroviral chez des personnes vivant avec le VIH et traités pour tuberculose.

Introduction :

Chez les personnes vivant avec le VIH (PVVIH) à un stade avancé de la maladie, les taux de succès virologique peuvent être inférieurs à ce qui est habituellement observé lorsque l'infection VIH est traitée à un stade précoce. L'essai Reflate TB2 a échoué à montrer la non-infériorité du raltegravir par rapport à l'efavirenz chez les PVVIH atteintes de tuberculose. Notre objectif était d'identifier les facteurs associés au succès virologique et à une meilleure adhésion au TARV.

Méthodes : Dans cette analyse, nous avons inclus les participants randomisés dans l'essai Reflate TB 2 pour lesquels les données d'adhésion au traitement étaient disponibles. Le critère de jugement principal était le succès virologique (ARN VIH < 50 copies/mL) à la semaine 48 et le critère de jugement secondaire était l'adhésion au TARV telle qu'évaluée par le rapport entre le nombre de comprimés prescrits et le nombre de comprimés rapportés à la pharmacie. Nous avons réalisé deux analyses distinctes en utilisant la régression logistique pour étudier les facteurs associés au succès virologique et à l'adhésion au TARV.

Résultats : 444 participants ont été inclus dans l'analyse. Au cours des 48 semaines du suivi, 290/444 (65 %) participants avaient une adhésion au TARV ≥ 95 %. À la semaine 48, 288/444 (65 %) participants étaient en succès virologique. Dans l'analyse multivariée, le sexe féminin (aOR 1,77 (IC à 95 % 1,16 – 2,72), $p=0,0084$), une charge virale VIH-1 plus basse à l'inclusion (< 100 000, aOR 2,29 (IC à 95 % IC 1,33 – 3,96), $p=0,0087$) et une adhésion au TARV ≥ 95 % (aOR 2,38 (IC 95 % 1,56 – 3,62), $p<0,0001$), étaient indépendamment associés au succès virologique. Le nombre quotidien de comprimés du TARV était le seul facteur associé à une adhésion au TARV ≥ 95 % (OR 0,81 (IC à 95 % 0,71-0,92), $p = 0,0018$).

Conclusions : Chez les PVVIH avec tuberculose recevant un TARV comprenant le raltégravir ou l'efavirenz, le sexe féminin, l'adhésion optimale au TARV et la charge virale <100 000 copies/mL à l'inclusion étaient associés au succès virologique. Le nombre de comprimés de TARV prescrits quotidiennement était le principal facteur prédictif de l'adhésion au traitement.

Différences de taux de succès virologique chez des personnes vivants avec le VIH traitées pour tuberculose dans 4 pays à ressources intermédiaires ou limitées.

Introduction :

Dans un essai de phase III incluant des PVVIH traitées une tuberculose les taux de succès virologique observés étaient plus faibles que ce qui est habituellement attendu. Une charge virale VIH-1 plus basse à l'initiation du traitement ainsi qu'une meilleure adhésion au traitement étaient associées à des taux de succès virologique plus élevés. Nous avons souhaité comparer les taux de succès virologique dans les différents pays ayant participé aux essais ANRS 12180 Reflate TB et ANRS 12300 Reflate TB2.

Méthodes :

Nous avons fusionné les données de deux essais cliniques randomisés évaluant le raltégravir et l'éfavirenz chez des PVVIH traitées pour une tuberculose au Brésil, en Côte d'Ivoire, au Mozambique et au Vietnam. Le critère de jugement principal était la proportion de participants en succès virologique à la semaine 48 (charge virale VIH-1 < 50 copies/mL) dans chaque pays. Nous avons évalué les facteurs associés au succès virologique par régression logistique.

Résultats :

550 participants ont été inclus dans cette analyse : 140 au Brésil, 170 en Côte d'Ivoire, 129 au Mozambique et 111 au Vietnam. Dans l'ensemble de la population, la médiane de charge virale VIH-1 était de 5,4 log₁₀ copies/mL et 362/550 (65,8 %) participants étaient en succès virologique à la semaine 48. Les taux de succès virologique étaient : 105/140 (75,0 %) au Brésil, 99/170 (58,2 %) en Côte d'Ivoire, 84/129 (65,1%) au Mozambique et 74/111 (66,7%) au Vietnam (p=0,0217). Dans l'analyse de non-infériorité en intention de traiter : 177/277 (63,9 %) patients sous raltégravir et 185/273 (67,9 %) patients sous éfavirenz avaient une charge virale VIH-1 plasmatique < 50 copies/mL à la semaine 48. La différence entre les taux de succès virologique à la semaine 48 entre les participants traités par raltégravir et éfavirenz était de -3,9% (-11,8% ; 4,1%), répondant ainsi au critère de non-infériorité. Chez les participants recevant du raltégravir, la proportion de participants en succès virologique était de 55/70 (78,6 %), 48/86 (55,8 %), 40/65 (61,5 %) et 34/56 (60,7 %) au Brésil, en Côte d'Ivoire, au Mozambique et au Vietnam, respectivement (p=0,0247); chez les participants recevant l'éfavirenz la proportion de succès virologique à S48 était de 50/70 (71,4%), 51/84 (60,7%), 44/64 (68,7%) et 40/55 (72,7%) au Brésil, en Côte d'Ivoire, au Mozambique et au Vietnam, respectivement (p=0,3931).

À la semaine 48, 397/550 (72,2 % ; 95 % IC 68,4 %-75,9 %) participants avaient une charge virale VIH-1 < 200 copies/mL et 407/550 (74,0 % ; 95 % IC 70,3 %-77,7 %) participants avaient une charge virale VIH-1 < 1 000 copies/mL. Dans l'analyse multivariée, le niveau de charge virale à l'initiation du TARV était indépendamment associé au succès virologique : ARN du VIH-1 < 100 000 copies/mL OR : 3,12

(IC à 95 % : 1,94 ; 5,01) et ARN du VIH-1 : 100 000 -499 999 copies/mL OR : 1,80 (IC à 95 % 1,19 ; 2,73).

Conclusions :

Il existait des différences de taux de succès virologique entre les quatre pays participant aux essais ANRS 12180 Reflate TB et ANRS 12300 Reflate TB2 et cela était expliqué par le niveau de charge virale avant le traitement. Chez les PVVIH se présentant à un stade avancé de l'infection VIH, l'analyse des données des programmes nationaux VIH et tuberculose sont nécessaires pour mieux documenter la réponse virologique sous TARV.

Discussion/Conclusion

Chez les PVVIH atteinte de tuberculose qui débutent un TARV à un stade tardif de l'infection VIH avec une charge virale pré-thérapeutique élevée, le taux de succès virologique à un an est plus faible qu'attendu, notamment dans les pays à ressources limitées. Dans ce contexte, une adhésion parfaite au TARV est essentielle pour atteindre le succès virologique et limiter le risque d'échec, avec émergence potentielle de résistance au TARV. Les schémas thérapeutiques comprenant l'éfavirenz restent les plus efficaces dans les essais de non-infériorité évaluant les TARV pour le traitement des PVVIH avec tuberculose. Les résultats présentés dans cette thèse, démontrent que le raltégravir semble être une alternative acceptable, mais uniquement chez certain patient avec une charge virale pré-thérapeutique de moins de 100 000 copies/mL, avec une excellente adhésion au TARV, et probablement si la durée d'utilisation du raltégravir se limite à la durée du traitement antituberculeux.

L'évaluation de nouvelles combinaisons ARV doit se poursuivre pour traiter les PVVIH avec tuberculose, en particulier avec la mise à disposition de nouvelles voies d'administration du TARV avec des molécules injectables à longue durée d'action, et également l'arrivée de nouveaux traitements antituberculeux. Dans l'attente que ces études soient réalisées, les données provenant de grandes cohortes dans les pays à revenus faibles ou intermédiaires devraient fournir des informations sur l'efficacité du TARV comprenant le dolutégravir, désormais recommandé par l'OMS. Il est nécessaire d'améliorer la surveillance virologique de l'infection VIH via la mesure de la charge virale au cours de la première année suivant l'initiation du TARV. Cela permettrait d'identifier l'échec virologique le plus tôt possible, en particulier chez les PVVIH se présentant à un stade avancé de l'infection VIH, permettant ainsi la mise en place de mesures pour améliorer l'adhésion au traitement.

List of personal publications and scientific communications on the topic

Articles in peer-reviewed journals

Published¹:

Grinsztejn B, **De Castro N**, Arnold V, Veloso VG, Morgado M, Pilotto JH, Brites C, Madruga JV, Barcellos NT, Santos BR, Vorsatz C, Fagard C, Santini-Oliveira M, Patey O, Delaugerre C, Chêne G, Molina JM; ANRS 12 180 Reflate TB study group. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis* 2014;14:459-67

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Submitted:

N. De Castro, C. Chazallon, C. Brites, E. Messou, C. Khosa, D. Laureillard, G. Do Chau, H. Pilotto, S. Eholie, C. Delaugerre, JM. Molina, L. Wittkop, B. Grinsztejn, O. Marcy. Differences in virologic response to antiretroviral therapy in people with HIV treated for tuberculosis in 4 high-TB burden countries – a pooled analysis of two randomized controlled trials. Submitted to *AIDS*

Oral communications

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N. De Castro, O. Marcy, C. Chazallon, E. Messou, S. Eholie, N. Bhatt, C. Khosa, D. Laureillard, G. Do Chau, V. Veloso, C. Delaugerre, X. Anglaret, JM Molina, B. Grinsztejn for the ANRS 12300 Reflate TB2 study group. Virologic efficacy of raltegravir vs. efavirenz based antiretroviral

¹ The work published in the papers Grinsztejn *et al.* Lancet ID 2014 and Kherabi *et al.* JAIDS 2022 is not presented in the thesis but both articles are provided in the appendix 1 and 2.

treatment in HIV1-infected adults with tuberculosis W48 results of the ANRS 12300 Reflate TB2 trial. 10th IAS conference. Mexico 2019. Slides MOAB0101

Marcy O, **De Castro N**, Chazallon C, Messou E, Eholie S, Bhatt N, Khosa C, Laureillard D, Do Chau G, Veloso V, Delaugerre C, Anglaret X, Grinsztejn B, Molina JM for the Reflate TB2 study group. Adherence and factors associated with virologic success in HIV-1 infected adults with tuberculosis receiving raltegravir or efavirenz in the ANRS 12300 Reflate TB2 trial. 23rd International AIDS conference virtual 6-10 July 2020. Abstract OAB0303

Posters

De Castro N, Chazallon C, Messou E, Eholie S, Bhatt N, Khosa C, Laureillard D, Do Chau G, Veloso V, Delaugerre C, Anglaret X, Molina JM, Grinsztejn, Marcy O, ANRS 12300 Reflate Tb2study group et al. Factors associated with high adherence in HIV-1 infected adults with tuberculosis receiving raltegravir or efavirenz- based antiretroviral therapy in the ANRS 12300 Reflate TB2 trial. 18th European Aids Conference, London October 27-30, 2021. Abstract PE2/59

C. Khosa, C. Chazallon, H. Perazzo, I. Massango, E. Messou, S. Eholié, D. Laureillard, G. Do Chau, X. Anglaret, J.-M. Molina, B. Grinsztejn, O. Marcy, **N. De Castro**, ANRS 12300 Reflate TB2 Study Group. Incidence and risk factors for liver enzyme elevation in HIV-1 infected patients treated for tuberculosis: a secondary analysis of the multi-country ANRS 12300 REFLATE TB2 trial. 24th International AIDS Conference, Montreal, 29 July to 2 August 2022

Introduction

Tuberculosis (TB) remains the leading cause of death among people with Human Immunodeficiency Virus (HIV), representing up to 30% of AIDS related deaths worldwide. In people with HIV (PWH) with TB, management of treatment-related adverse events is more complex because antiretroviral therapy (ART) and drugs used for TB treatment share common side effects and because it is not always easy to identify the causative drug in case of rash or hepatotoxicity. Also, drug-drug interactions between antiretrovirals and the combination of drugs used to treat TB, especially rifampicin, leave only few options for ART.

The latest World Health Organization (WHO) guidelines for low- and middle-income countries (LMICs), recommend to use the second-generation integrase strand transfer inhibitor (INSTI) dolutegravir for all PWH since 2018 and to double the dose in case of tuberculosis. Until then, the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz was the drug of choice, in association with two nucleoside reverse transcriptase inhibitors (NRTIs) for ART in PWH treated for tuberculosis. To date, no other alternative has proved to perform as well in a non-inferiority randomised clinical trial. As there were few options that could be used to replace efavirenz, it was a challenge for TB and HIV programs worldwide to provide guidance to the clinicians. In this context, there was a need to evaluate newer antiretroviral drugs to provide alternatives for patients in whom efavirenz use was impossible, due to intolerance or resistance. Raltegravir was the first integrase strand transfer inhibitor (INSTI) approved for the treatment of HIV and also the first to be evaluated for the treatment of PWH treated for tuberculosis.

The objective of my thesis was to evaluate if raltegravir could be proposed for the treatment of HIV infection in PWH treated concomitantly for TB. The hypothesis was that raltegravir used at the standard dose of 400 mg twice daily could be used as part of an ART regimen to treat ART naïve PWH with TB. In the first part of this thesis, I present an overview of tuberculosis and a review of the main issues in the concomitant management of HIV infection and tuberculosis. I then presented the results of the three studies conducted as part of my thesis. First, the results of the ANRS 12 300 Reflate TB 2 trial evaluating the non-inferiority of raltegravir versus efavirenz. The second study analysed factors associated to virologic success and ART adherence in PWH concomitantly treated for TB. The third study evaluated the differences in virologic success rates between the countries who participated to the Reflate TB phase II and Reflate TB 2 phase III trials. To complement data from the two clinical trials, we had planned to analyse real-life data from national programs. The objective was to evaluate the virologic efficacy of raltegravir, dolutegravir or efavirenz-based regimens in PWH treated for TB within the Brazilian national HIV and TB programs. Due to the Coronavirus Disease-2019 (COVID-19) pandemic, this project was delayed but analysis is planned to start before the end of 2022. Finally, in the general

discussion of the thesis, I discussed how this work questions the current antiretroviral therapy guidelines in PWH treated for tuberculosis and future perspectives.

1 Tuberculosis: the essentials.

1.1 Epidemiology of tuberculosis

In 2020, the WHO estimated that 9.9 million persons fell ill with tuberculosis and that 1.5 million (15%) died from the disease [1]. Approximately 5 million cases were attributable to five risk factors: undernourishment, HIV-infection, alcohol use disorders, smoking and diabetes. The provisional estimations suggested that due to the COVID-19 pandemic, the global number of TB-related deaths increased between 2019 and 2020 and that there was an 18% drop in the report of people newly diagnosed with TB [1]. Before the COVID-19 pandemic, TB incidence decreased by about 2% per year globally, with a cumulative reduction of 11% between 2015 and 2020. However, this is far from the objective of 20% reduction between 2015 and 2020 that had been set by the “End TB Strategy”, showing the gaps in the fight against TB. Moreover, only 58% of the estimated 9.9 million of TB cases were diagnosed and reported [1].

Eight countries account for 75% of TB cases reported (Bangladesh, China, India, Indonesia, Nigeria, Pakistan, Philippines, and South-Africa) and 30 countries are considered as high burden countries [1].

Maps and graphs summarizing TB epidemiology are reported in Appendix 3.

1.2 The origins of tuberculosis

Tuberculosis is an infectious disease that has affected humans for probably 70,000 years and is caused mostly by three mycobacteria: *Mycobacterium (M.) tuberculosis*, *M. africanum* and *M. bovis*. These three mycobacteria are present in all parts of the world, they are closely related and belong to the *Mycobacterium tuberculosis complex* (MTBC), along with other animal-specific mycobacteria. As *M. tuberculosis* is the cause of the vast majority of TB cases, *M. tuberculosis* will be referred as the agent of tuberculosis throughout this manuscript.

The origin of *M. tuberculosis* is debated, and the hypothesis of animal-to-human transmission 10,000 years ago with the development of agriculture has been questioned after the discovery of tuberculosis-like disease in a *Homo erectus* fossil from the palaeolithic, way before animal domestication [2]. The identification of rare cases of human tuberculosis related to *M. canettii*, all occurring in a limited region of Africa led to another hypothesis. This mycobacterium has more genetic diversity than other members of MTBC, has the ability of horizontal gene exchange, and interestingly, no human-to-human transmission of *M. canettii* has been described. The hypothesis is that *M. canettii* and MTBC share a common ancestor originating from the horn of Africa with a potential environmental reservoir. This

ancestor might have migrated along with modern humans, with a subsequent separate co-evolution of the human host and the pathogen in each region of the world [2,3].

It was only in the nineteenth century that TB transmission and its causative agent were discovered. Villemin demonstrated that tuberculosis was a transmissible disease in 1865 by inoculating a rabbit with purulent liquid from a tuberculous cavity and he later hypothesised that the transmission was airborne [4]. Koch identified the bacteria that would be called tubercle bacillus as the agent responsible for TB in 1882 [5]. The Bacille Calmette et Guérin (BCG) vaccine was discovered in 1908 and first inoculated 100 years ago in a new-born. The first vaccination campaign in infants started in the 1920's in France and became mandatory in most European countries after the 1950s [6].

1.3 From *M. tuberculosis* infection to active tuberculosis disease

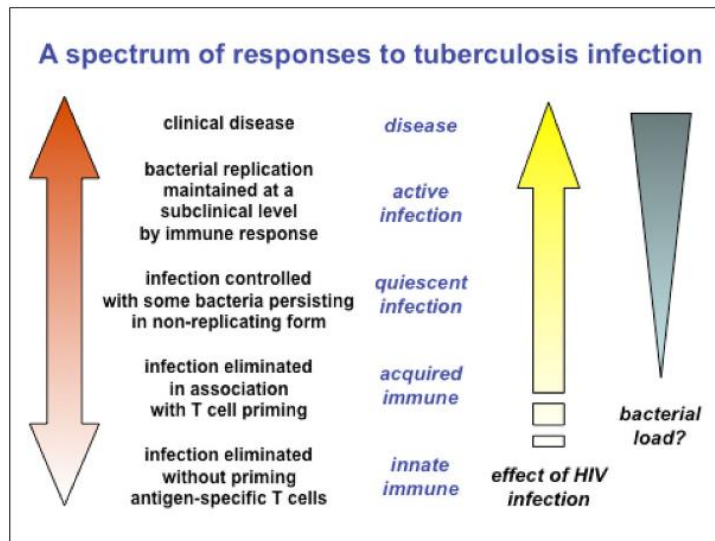
The transmission of *M. tuberculosis* is inter-human and airborne via aerosolization [7]. In high TB burden settings, it is estimated that more than 80% of transmission occur outside of the household, in schools, public transportation, workplaces, healthcare facilities, mines, and prisons [8]. Epidemiological studies conducted in the 1960s suggested that a minority of individuals were responsible for the majority of transmissions, and this has been confirmed in animal and human studies [9–11].

After contact with a contagious person affected by pulmonary TB, it is estimated that 30% of contacts will become infected and that only 10% will develop active disease during their lifetime, mostly within the first 2 years after infection. Indeed, after infection, the immune system is usually able to contain *M. tuberculosis* in the lung within a structure formed by immune cells called granuloma, and the individual infected remains free of symptoms. This is called tuberculosis infection (TB infection) or latent tuberculosis infection (LTBI) [12]. If the granuloma is unable to contain *M. tuberculosis*, the local evolution of the infection can lead to pulmonary disease within weeks and cause active TB disease. It seems that, not only is the granuloma an immunological shield containing the mycobacteria as it was already well known, but that it also provides favourable conditions for mycobacteria replication through the dynamics of the cells present within the granuloma [13].

It is estimated that a quarter of the world population is infected with *Mycobacterium tuberculosis* [14]. The vast majority of cases are TB infections/LTBI that will never evolve to active tuberculosis. Recent advances in understanding TB infection physiopathology suggest that most TB cases result from recent infection, and only in certain circumstances from reactivation, as during therapy with tumour necrosis factor (TNF) inhibitors. The denomination TB infection rather than LTBI is now preferred as it is probably more accurate and does not imply the binary explanation for TB with only two states that would be latent infection and active TB disease. The spectrum of TB infection seems to be a continuum between asymptomatic quiescent TB infection and active symptomatic TB (figure 1) [12]. The challenge

is to identify people at higher risk of evolution towards active TB disease in the pre-symptomatic phase of the infection and treat them before they develop symptoms and become contagious.

Figure 1 : Tuberculosis infection spectrum (adapted from Barry *et al.*[12])



The diagnosis of TB infection is indirect, based on immunological tests, only confirming that the immune system has been previously exposed to *M. Tuberculosis* (or other mycobacteria) and that the subject tested is immunocompetent. The first immunological test to be used was the tuberculin sensitivity test (TST also known as Mantoux test) that consists of intradermal injection of Purified Protein Derivative (PPD) isolated from *M. tuberculosis* cultures and subsequent measurement of the skin reaction 48-72 hours later. The induration measured is the consequence of immune responses mediated by T lymphocytes. TST lacks specificity due to cross reaction with non-tuberculous mycobacteria and BCG vaccination. Interferon gamma (IFN- γ) releasing assays (IGRA) are *in vitro* tests that measure the production of IFN- γ in the presence of *M. tuberculosis* antigens, with better specificity. None of these tests allow the identification of viable mycobacteria and they do not discriminate between TB infection and active TB disease. Both TST and IGRA lack sensitivity to identify TB infection in immunocompromised persons or in young children [12,14,15]. Depending on their availability, both tests are recommended to diagnose TB infection in specific populations that may require tuberculosis preventive treatment, particularly household contacts of pulmonary TB, healthcare workers or immunocompromised persons [16,17].

Several host factors facilitate TB infection and/or accelerate the evolution towards active TB disease: age below 5 years, immunosuppression especially due to HIV infection, malnutrition. Targeted testing for TB infection is recommended in these populations [16].

1.4 Diagnosis of active tuberculosis

The most classical manifestation of TB active disease is pulmonary TB, presenting with cough that may be associated with weight loss and night sweats lasting for several weeks or months [18]. After infecting the lung, *M. tuberculosis* can migrate to other organs and TB can affect all organs. The second most frequent tuberculosis presentation is peripheral lymphadenopathy, with cervical localisation in the majority of cases. Vertebral tuberculosis (also named Pott's disease) is another typical form of TB, less frequent but with potential severe neurological disability. The most severe forms are disseminated TB or TB meningitis, affecting particularly infants and immunocompromised people [18].

Active TB diagnosis is based on the identification of *M. tuberculosis*. As for other bacteria, the techniques for *M. tuberculosis* isolation are based on microscopic examination (performed a few hours after the sample arrives at the lab), culture (2 to 6 weeks according to the technique used), and molecular testing. Mycobacteria are acid-fast bacilli (AFB) that are visualized thanks to their biochemical properties in sputum smears with direct microscopic examination [19].

As the majority of patients with TB have pulmonary disease, the most frequently collected samples for diagnostic purposes are expectorated sputum samples. When direct microscopic examination on sputum samples is positive, TB is smear-positive or AFB-positive. Smear-positive pulmonary TB usually has high bacillary load, and represents the most contagious form of the disease. Generally, smear positive TB will present with typical pulmonary cavitory lesions on chest X-ray [20,21]. Lung cavities provide an ideal environment for mycobacteria growth with high bacillary loads in patients with cavities [22]. Approximately 50-60% of pulmonary TB are smear positive, when laboratory facilities are well equipped to performed microscopy [23]. Smear negative but culture positive pulmonary TB cases usually have limited pulmonary lesions and thus lower bacillary load compared to smear positive cases with cavities. Still, they can be contagious and participate to transmission, although less than individuals with smear positive pulmonary TB [8,24]. Without proper treatment, most patients with smear negative pulmonary TB will develop more extensive disease [24].

For decades, the diagnosis of pulmonary TB relied on direct microscopic examination of sputum smears and cultures. One limitation for TB diagnosis using microscopic examination is that some persons are not able to produce sputum, especially children. Cultures with drug susceptibility testing (DST) require facilities and human resources that are only available in high income countries This was an important limitation for tuberculosis diagnosis and also drug susceptibility testing to detect the presence of resistance to anti-tuberculosis drugs. In 2010, only 53% of clinics receiving patients with TB in Africa had access to cultures [25]. This represented a huge gap for TB diagnosis and resistance testing. Since then, commercial diagnostic tests based on nucleic acid amplification (NAAT) were developed and were recommended by the WHO to facilitate both the identification of *M. tuberculosis* and the identification of resistance to the first line antibiotics used to treat tuberculosis [25,26]. The most widely used is the

Xpert MTB/RIF test (Cepheid®) that needs minimal lab infrastructure and sample processing, providing same day (few hours) results [25-27]. A recent meta-analysis showed that using Xpert MTB/RIF did not increase the number of people treated nor reduced all-cause mortality, although it may reduce mortality among PWH (moderate certainty evidence). It also showed that using Xpert MTB/RIF increased bacteriological confirmation of TB (moderate certainty evidence) [28]. However, according to the WHO TB report, in 2020 the rate of microbiologic confirmation overall was only 59% among the pulmonary TB cases that were notified both in people with and without HIV. This proportion of confirmed pulmonary TB is stable since 2005 [1]. The WHO also reported that a rapid molecular test was used as the initial diagnostic test in only in one third of people newly diagnosed with TB in 2020, with important regional disparities [1].

1.5 Tuberculosis treatment

It was estimated that in the pre-antibiotic era, untreated smear positive TB among persons without HIV had a 10-year case fatality between 53% and 86%, and it was approximately 20% for smear-negative culture-positive TB. The duration of TB disease from onset of symptoms to cure or death was 3 years and appeared to be similar for smear-positive and smear-negative tuberculosis [29]. The prognosis changed dramatically following the introduction of effective TB treatment in the 1950s [30].

In the early years of TB therapy, different reports showed that treatment with a single drug resulted in high rates of resistance and subsequent failure when retreatment was necessary. This was the rationale to evaluate an association of multiple drugs to prevent emergence of resistance.

1.5.1 Treatment of drug-susceptible tuberculosis

The treatment of active tuberculosis is based on a combination of different bactericidal and bacteriostatic drugs. The total duration of treatment for drug susceptible TB is six months except for vertebral tuberculosis or meningitis that require 9-12 months of treatment [31]. Studies conducted between the mid-1940s and the mid-1980s, were key to determine the standard tuberculosis treatment that is still in use today [30]. Since the 1990s, the standard anti-TB therapy consists of a combination of the four first-line anti-TB drugs isoniazid, rifampicin, pyrazinamide and ethambutol during the first 2 months (intensive phase) followed by four months of isoniazid and rifampicin (consolidation phase)[31]. This regimen applies only for drug susceptible tuberculosis and if all drugs can be used.

Isoniazid and rifampicin, are the cornerstones of TB treatment; both have rapid bactericidal activity and reduce the bacterial load rapidly. Rifampicin and pyrazinamide are the best sterilizing drugs to prevent post-treatment relapse [30,32,33]. The combination of isoniazid, rifampicin and pyrazinamide allowed

to shorten the overall duration of treatment from 12-18 months when older regimens without rifampicin and/or pyrazinamide were used, to “only” six months. It was shown that prolonging treatment with pyrazinamide for more than 2 months did not change relapse rates, whereas if rifampicin was not used during the whole course of treatment, relapse rates were higher [30].

Trials evaluating intermittent administration of an association of rifapentine, a long acting rifamycin, in combination with isoniazid showed acceptable relapse rates in people without HIV [30]. The rationale to propose intermittent regimens was that it would be easier to monitor drug intake when directly observed therapy (DOT) programs were implemented, however daily treatment is preferred to intermittent treatment in most guidelines [31,34,35].

Several clinical trials evaluated if using fluoroquinolones would allow to shorten TB treatment to four months. Fluoroquinolones were used either in addition to the standard TB treatment or to replace ethambutol. All had failed to show the non-inferiority of the shorter regimen compared to the 6 months treatment [36]. Moore recently, the Tuberculosis Trials Consortium Study 31 (study 31/ A5349) from the AIDS Clinical Trials Group (ACTG) showed that it was possible to reduce the duration of treatment to four-months in adults [37]. The new regimen consisted of rifapentine (replacing rifampicin), isoniazid, pyrazinamide, and moxifloxacin (replacing ethambutol and used for the whole duration of TB treatment), and was non inferior to the usual six-month treatment [37]. The advantage of shortening treatment by 30% is obvious for national programs, but there are some drawbacks to the generalizability of this shorter regimen. First, rifapentine is not available in many countries, including European countries where the drug is not approved. The cost of rifapentine needs to be reduced and generics made available so LMICs can purchase it. The massive use of fluoroquinolones may facilitate emergence of resistant bacteria from the human microbiomes with potential hard to treat bacterial infections. There is also an important risk of emergence of fluoroquinolone resistant TB in the years following the widespread use of this shorter regimen, which may jeopardize their use for resistant TB. Finally, as acknowledged by the WHO, at this point this regimen cannot be recommended in certain sub-groups that were not enrolled in the pivotal trial: people weighing less than 40 kg, people with extra-pulmonary TB (TB meningitis, disseminated TB, osteoarticular TB, abdominal TB), PWH with a CD4+ T-cell counts (CD4 counts) less than 100 cells/mm³, children less than 12 years of age and pregnant, breastfeeding and postpartum women [31].

One other question about standard TB treatment is whether optimal doses of rifampicin are being used. Several pharmacokinetic studies have explored this question and showed that doses as high as 40 mg/kg/day were associated with increased bactericidal activity and were well tolerated [30, 38–40]. Using higher doses of rifampicin may allow to shorten the duration of TB treatment but this remains to be demonstrated. Also, it is not clear whether the use of increased rifampicin reduces mortality. Results from 2 clinical trials on TB meningitis are conflicting with this regard. One Indonesian phase II study

enrolling 60 patients suggested that survival was better when intravenous high dose rifampicin was used for the first 2 weeks of TB treatment in patients with severe illness [41]. However, in a large phase III trial enrolling more than 800 patients with TB meningitis in Vietnam, oral rifampicin at the dose of 15 mg/kg daily did not result in higher survival [42].

New drugs or new combinations are in the pipeline and are being evaluated in phase I, II or III studies to treat both sensitive and resistant TB (figure S1, appendix 4). The Simplifici TB trial (NCTNCT03338621) is a phase II/III trial evaluating the use of the same 6-month regimen to treat both drug susceptible and drug resistant TB using bedaquiline, pretomanid, moxifloxacin and pyrazinamide (BPaMZ). The Truncate TB trial (NCT03474198) is evaluating different 2 months regimens with newer TB drugs (bedaquiline) or repurposed drugs (linezolid) or already developed TB drugs used at higher doses (clofazimine or rifapentine). The interest of these 2 trials is that the regimens evaluated are not prone to drug-drug interactions.

1.5.2 Definition of treatment outcomes

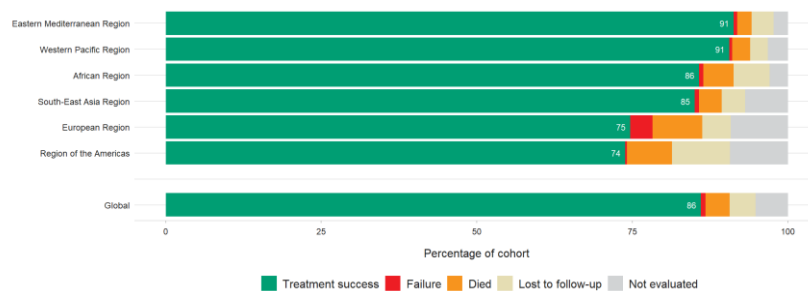
Since the introduction of TB treatment with national programs, the WHO has developed and promoted definitions of TB treatment outcomes, based on clinical evolution on treatment and bacteriological data. These definitions are pragmatic and are used in both high- and low-income countries in a public health approach. At the end of TB treatment, patients are reported in one of the following categories [43]:

- Cured: bacteriologically confirmed tuberculosis at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
- Treatment completed: patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
- Treatment failed: patient whose sputum smear or culture is positive at month 5 or later during treatment.
- Died: patient who dies for any reason before starting or during the course of treatment.
- Lost to follow-up: patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
- Not evaluated: patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Although important for programmatic purposes, these definitions have some caveats. First, many patients are unable to produce sputum after a few weeks of treatment, it is thus difficult to meet the

bacteriological definition for cure. Secondly, missing data are common, particularly in high income countries (figure 2). For example, in France, the outcome is unknown at the end of TB treatment for 15 to 20 % of patients treated for TB [44–46]. Also, relapse may occur after the end of TB treatment, so an evaluation at least 12 months after the end of treatment would be more accurate. Some authors suggest that the time without relapse might be a better indicator of treatment success, but this would need to define after which time point a patient is considered definitely cured [47].

Figure 2: Treatment outcomes for new and relapse TB cases in 2019, WHO regions and globally [1].



1.5.3 Drug resistant tuberculosis

The most frequent resistance is isoniazid resistance. In case of isoniazid monoresistance, treatment outcomes may not be changed but there is a risk of emergence of further resistance, especially to rifampicin, the most important TB drug to reduce treatment duration ensuring low relapse rates. This is the rationale for all international guidelines to recommend the use a four-drug combination with ethambutol as a companion drug to rifampicin in case of isoniazid resistance, pending the results of drug susceptibility testing when available, or for the whole duration of the intensive phase of treatment [31,34,35].

In case of intolerance or resistance to one or more drugs, treatment duration must be adapted. For instance, if pyrazinamide cannot be used, the consolidation phase must be extended to achieve an overall duration of treatment of 9 months. If rifampicin cannot be used, treatment duration is 12 to 18 months [30,34].

The emergence of drug resistance results from many factors, including bacterial specificities as high minimum inhibitory concentrations (MICs), but more frequently the reason is sub-optimal treatment of drug-susceptible TB. The use of sequential mono- or dual therapy was associated with high rates of relapse and drug resistance but with the implementation of regimens combining isoniazid, rifampicin,

pyrazinamide with or without ethambutol, the emergence of resistance became rare, especially with the use of fixed dose combination tablets [30]. Sub-optimal concentrations of TB drugs is another driver for the emergence of resistance with the potential impact of pill burden on adherence to TB treatment [32]. Finally, the low quality of the combinations used was also found to explain important variability of drug exposure [48]. The WHO prequalification process is important to guarantee that the combinations purchased by countries and distributed within TB programs are not substandard or falsified medicines [49].

Multidrug-resistant TB (MDR-TB) is defined by resistance to at least isoniazid and rifampicin. Extensively drug resistant tuberculosis (XDR-TB) is an MDR-TB with additional resistance to fluoroquinolones and another drug from the list of second line drugs that are active against *M. tuberculosis* (i.e linezolid or bedaquiline)[50]. These two patterns of resistance are grouped under the denomination multidrug resistant/rifampicin resistant-TB (MDR/RR-TB). In some areas of the world, the burden of MDR/RR-TB is an important issue representing up to 20-50% of TB cases that are diagnosed. It is estimated that in 2018-2020, 483,000 cases of MDR/RR-TB were treated globally but it represented only 32% of the estimated MDR/RR-TB cases overall [1].

Before the availability of new drugs to treat MDR/RR-TB, treatment was individualized. The choice of the drugs was based on the availability of second line drugs in the countries, previous exposure to second line drugs (especially fluoroquinolones) and drug susceptibility testing when available. These regimens consisted of an association of second-line drugs for a prolonged duration (18 to 24 months) with many side effects, high pill burden and treatment success rates were, at best, 50-60% [1, 51].

A shorter regimen (9-11 months), known as the Bangladesh regimen, using high-dose moxifloxacin, clofazimine, ethambutol, and pyrazinamide administered over nine months, with kanamycin, high doses isoniazid, and prothionamide in the first four months was non inferior to the WHO standard of care (WHO SoC) regimen [52]. However, patients with XDR-TB were not eligible to such regimen as they harbour resistance to fluoroquinolones and aminoglycosides. Another 9-12 months all oral regimen based on the Bangladesh regimen where bedaquiline replaced injectable kanamycin has been used since 2017 in South Africa with a 73% treatment success rate, compared to 60% with standard of care [51]. More recently, the Nix and ZeNix trials (two small single-group studies) as well as the TB PRACTECAL trial (multi-arm randomized clinical trial) showed that all-oral 6-months regimens with bedaquiline, pretomanid and linezolid, with or without moxifloxacin (BPaLM or BPaL), resulted in only 10% of unfavourable outcomes in patients with MDR/RR-TB [53–55].

Following these results, the WHO released a rapid communication in 2022 stating that the 6-month BPaLM regimen may be used programmatically in place of 9-month or longer (>18 months) regimens [51,56].

1.6 Biomedical prevention of tuberculosis and beyond

The biomedical prevention of TB is based on vaccination and TB preventive therapy (TPT).

The vaccination of all children at birth is recommended in countries where tuberculosis is highly endemic. BCG vaccination remains the most important prevention measure in countries with high TB burden. It is estimated that 88% of children worldwide received the vaccine during their first year of life in 2019 [6]. It is not recommended to administer a booster vaccine later in life. In countries with a low prevalence of TB, BCG vaccination may be proposed only to high-risk neonates originating from high endemic countries, as it is the case in France. BCG has a 70% efficacy to reduce pulmonary, disseminated TB and TB meningitis in neonates and young children but fails to substantially reduce TB incidence in adults and to prevent TB infection or *M. tuberculosis* latency [6, 57, 58]. Strategies using BCG but with modified immunization schedules (prime-boost strategy using different BCG boosters) or different routes of administration (mucosal or intravenous instead of intradermal) showed promising results to enhance and prolong immune responses against *M. Tuberculosis* [59].

Another strategy to prevent the development of active TB is to provide tuberculosis preventive treatment (TPT) in special populations. The WHO recommends TPT in people suspected to have TB infection and are at high risk of developing active TB as for example, but not limited to, people with HIV or household contacts of persons with pulmonary TB, especially younger children [60].

Isoniazid preventive (IPT) therapy was the first strategy used and resulted in a 60% reduction of tuberculosis cases in household contacts in Alaska in the late 1950s [61]. Since then, other studies have shown that TPT prevented the development of active TB [62]. There are currently six regimens recommended as TPT: 6 or 9 months of daily isoniazid monotherapy, four months of daily rifampicin (4R), three months of daily rifampicin plus isoniazid (3HR), three months of rifapentine plus isoniazid weekly (3HP) and one month of rifapentine plus isoniazid daily (1HP) [16].

Interestingly, in Europe and North America, the burden of TB had substantially decreased before the introduction of systematic BCG vaccination and the introduction of TB drugs. Fighting poverty, malnourishment and overcrowded housing, as well as providing a better access to universal health care will change the burden of TB much more radically and quickly than biomedical interventions.

2 Tuberculosis in adults with HIV

HIV infection and tuberculosis are major pandemics with the same geographical distribution in many areas of the globe, particularly Sub-Saharan Africa, Asia or South America. There are many challenges for the concomitant management of these two linked epidemics. Clinical presentation of pulmonary tuberculosis is atypical in severely immunocompromised patients, leading to late diagnosis and often disseminated disease. Bacteriological diagnosis is also more difficult because PWH have pauci-bacillary TB. TB treatment failure, relapse and death are more frequent in persons with low CD4+ T cell counts, particularly in patient not receiving ART. Treatment of both conditions lead to higher pill burden, there are drug-drug interactions between antituberculosis treatment and antiretroviral therapy (ART) as well as overlapping toxicities. Finally, the worsening of tuberculosis lesions after ART introduction despite appropriate antibiotic treatment, known as immune restoration inflammatory syndrome (IRIS) is frequent and may be complex to manage in some patients. Other important issues are the risk of re-infection in regions where both TB and HIV infection are highly endemic, and the increased risk of acquiring drug resistant tuberculosis for most immunocompromised PWH.

2.1 Epidemiology of TB/HIV co-infection

Among the 9.9 million persons who fell ill with tuberculosis in 2020, 8% were PWH. Despite progress in access to ART and TPT, improvement in TB diagnosis with NAAT, TB remains the number one killer of PWH. Overall 31% of HIV-related deaths were due to TB [1]. The burden of HIV-TB co-infection disproportionately affects Africa: at least 70% of the world's TB cases in PWH were diagnosed in this region [1]. HIV prevalence among TB cases is the highest in Southern and Eastern African countries where 20 to 50% of TB cases are diagnosed in PWH, and is particularly high in South-Africa with more than 50% rates of HIV-infection in people with TB. In Eastern Europe, HIV infection is also common in persons with tuberculosis, with 20 to 50% prevalence of HIV infection among TB cases (figure S2 appendix 1) [1].

TB is a major contributor to hospitalization and in-hospital mortality among PWH in many settings all over the world but may go undetected/undiagnosed [63]. Autopsy studies conducted in Africa showed that 40-70% of PWH dying while hospitalized had undiagnosed TB and that disseminated disease was present in 60-90% of the cases [64–66]. Compared to people without HIV, the risk of developing tuberculosis in PWH increases rapidly after acquiring HIV infection and is the highest for patients with CD4 T-cell counts less than 200/mm³. After ART introduction, the risk of developing tuberculosis decreases but remains higher than that of people without HIV, with persistent risk of TB infection [67]. HIV-related immunosuppression plays a major role to accelerate the evolution from TB infection or sub-clinical TB to active disease. Individuals with immunodeficiency are also more susceptible to *M.*

tuberculosis infection. Finally, TB contributes to HIV disease progression by increasing HIV replication, immune activation and inflammation [68].

The WHO encourages countries to adopt specific public health strategies to decrease the burden of tuberculosis in PWH. These priorities are known as the three I's: Intensified case finding, Isoniazid preventive therapy and TB Infection Control. Most of these strategies have been implemented in countries highly endemic for tuberculosis leading to some advances in reducing TB related deaths, but gaps are still important to reduce the number of undiagnosed TB in PWH [60].

2.2 Tuberculosis diagnosis challenging in people with HIV

Atypical clinical presentation of pulmonary TB, lower bacterial load and limited lab facilities are barriers to tuberculosis diagnosis in PWH, especially in those with a higher degree of immunosuppression [18].

In 2011, the WHO recommended TB intensive case finding in PWH using a four-symptom screening strategy using a questionnaire to assess the presence of any of the following symptoms: current cough, fever, weight loss, or night sweats. In case of positive screening, rapid testing with Xpert MTB RIF on sputum was advised [60]. This recommendation was based on a large metanalysis showing that in outpatients, the sensitivity of the 4-question screening was 79% and the specificity was 50%, with a negative predictive value of 98% under the hypothesis of tuberculosis prevalence of 5% [69]. For PWH receiving ART, the sensitivity seemed to be lower at 50%, and negative predictive value was 96% considering a TB prevalence of 5% [70].

The limited accuracy of the 4-symptom screening rule was confirmed in hospitalized patients with HIV in a recent meta-analysis by the WHO published earlier this year. There was no added value to screen with the 4-symptom rule before testing with Xpert MTB RIF [71]. The recommendation has been adapted and is now to perform rapid tuberculosis diagnostic testing with Xpert MTB RIF in all inpatients with HIV, regardless of presence of symptoms in settings with high TB burden (TB prevalence at least 10%). A clinical trial conducted in South-Africa confirmed that universal testing with Xpert increased TB diagnosis by 17% every month [72]. This strategy, however, may still miss many TB cases stressing the need to continue to combine different strategies based on symptom screening, chest X ray or urine lipoarabinomannan (see below) [73–75].

In patients with moderate immunodeficiency ($CD4 > 350/mm^3$) the clinical and radiological presentation of TB is similar to that of non-immunocompromised patients, with a predominance of pulmonary tuberculosis. Typical chest X-ray lesions are apical lesions, with or without cavitation [67]. Conversely, PWH with $CD4$ -T cell counts $< 200/mm^3$, usually present with mild pulmonary symptoms leading to late diagnosis and disseminated disease in up-to 70-80% of cases, especially in patients with $CD4$ -T cell counts $< 100/mm^3$ as shown by autopsy studies [76,77]. Cavitory lesions are rare in very immuno-

compromised patients. Various radiological patterns have been described: diffuse (miliary) or bronchial localized micronodules, diffuse or localized infiltrates that can predominate in the lower lobes, mediastinal lymph nodes. Pleural effusion however is found in less than 5% of cases. Chest X-ray is normal in 10 to 20% of cases [67]. Radiological abnormalities are best identified with chest computed tomography but most patients do not have access to this technology in LMICs.

Given the frequency of smear negative TB in PWH, Xpert MTB RIF was first recommended in this population [24,67]. As already mentioned, using Xpert MTB/RIF increases bacteriological confirmation of TB and may reduce mortality among PWH [28].

The WHO also recommends to perform urine lipoarabinomannan (LAM) in PWH with low CD4 T cell counts who are seriously ill particularly patients with CD4 T cell count $<100/\text{mm}^3$ who are hospitalized with symptoms of TB or seriously ill patients regardless of CD4 T cell counts [73,78,79]. LAM is a lipopolysaccharide and the major component of *M. tuberculosis* cell wall. It is detectable in the serum and excreted in urine of people who have active TB [78]. Positive urine LAM is a predictor of mortality [80,81]. The major advantage of urine LAM is that it is a point-of care easy to use assay. The benefit of urine LAM detection to reduce mortality in PWH with CD4 count less than $100/\text{mm}^3$ was evaluated in two randomized trials conducted in Southern African countries and showed a 4-8% reduction in mortality [73,82,83]. Second generation LAM assays that are more sensitive may improve diagnosis in PWH with higher CD4 T cell counts and also in people without HIV [84].

2.3 Tuberculosis treatment in people with HIV

2.3.1 Tuberculosis treatment is not different in people with HIV

All international guidelines recommend to use the same standard four-drug regimen to treat TB in PWH and in people without HIV [31,34,85,86]. During the pre-ART era, extending treatment duration in PWH did not reduce mortality but relapse rates were reported to be higher [87,88]. One meta-analysis showed relapse rates were higher with shorter durations of rifamycins (<8 months) and in the absence of ART. Benefits of extending TB treatment were not clear either in patients already on ART at TB diagnosis [89]. Intermittent regimens are not recommended in PWH because relapse rates are also higher than with daily regimens [88–90]. There is a debate on whether higher doses of rifampicin may be necessary in PWH to improve treatment outcomes. This is further discussed in section 3.3.

In the study 31/ A5349 evaluating the shorter 4-months regimen with rifapentin and moxifloxacin, 194/2,516 (8%) participants were PWH with AFB or Xpert MTB/RIF positive TB. Participants were required to have CD4 counts above $100/\text{mm}^3$. As for the overall trial population, the shorter rifapentin-moxifloxacin containing regimen was non-inferior to the standard 6 months TB treatment in the

subgroup of PWH with culture positive TB [91]. However, the population of this sub-study may not be representative of the majority of PWH treated for tuberculosis : almost half of the PWH enrolled in the study were already on ART and virologically suppressed at baseline, and median CD4 counts were 344/mm³ (IQR: 223 - 455) [91]. Findings from this substudy will need to be confirmed in larger samples and in severely immunocompromised persons. In the 2022 WHO guidelines update, the shorter regimen was not recommended in PWH with CD4 T-cell counts <100/mm³ and in TB meningitis, osteoarticular TB or disseminated forms of TB [31].

2.3.2 Drug resistant TB in people with HIV

As for treatment of drug susceptible TB, treatment of MDR/RR-TB should not be different in PWH compared to people without HIV, but outcomes may not be as favourable as in people without HIV.

Intermittent anti-TB treatment was associated with TB relapse and emergence of TB drug resistance in PWH. Sub-optimal exposure to TB drugs, especially rifampicin, rifabutin or isoniazid were associated to the emergence of rifamycin resistance in different small studies [92–98]. Pharmacokinetic (PK) studies also suggest that drug concentrations were lower than the expected targets in PWH taking daily TB treatment which may be a risk factor for developing drug resistant TB [92]. Transmission of drug resistant tuberculosis to highly susceptible PWH with a low CD4 count can fuel the MDR/XDR epidemic in regions where both HIV infection and drug resistant tuberculosis are endemic. The rapid diagnosis of isoniazid and rifampicin resistance is therefore important to reduce ongoing transmission of resistant TB.

Mortality reported in PWH who have MDR/RR-TB was high before the availability of newer second-line drugs. Due to the delay in diagnosing resistance and the lack of appropriate TB treatment, during the XDR-TB epidemic that happened in KwaZulu Natal (South-Africa) between 2002 and 2008, almost all patients were co-infected with HIV and mortality was as high as 80% in PWH not receiving ART [99]. In a metaanalysis pooling studies published between 2009 and 2016 enrolling patients treated mostly during the 2000-2010 decade (but some studies enrolled patients treated in the 1990s), TB treatment outcomes were more favourable in people without HIV (68% treatment success and 9% deaths) compared to PWH on ART (55% treatment success and 29% deaths) and PWH not receiving ART (treatment success 34% and 26% deaths) [100]. In the same analysis, the use of bedaquilline, linezolid and fluoroquinolones were all associated with treatment success [100].

In the TB-PRACTECAL trial evaluating all oral bedaquilline containing regimens, 153 of 552 participants were PWH. The risk differences of unfavourable outcome between all shorter regimens and the WHO standard of care were not statistically significant but the tolerance profile was globally better

with all shorter regimens. These results differed from those in participants without HIV, with a higher difference between all shorter regimens and WHO standard of care. [76].

2.4 Tuberculosis preventive therapy in people with HIV

Before the ART era, several studies showed that treatment of TB infection reduced the risk of active TB in PWH, especially in those with a positive TST [101]. As testing for TB infection is complicated and may be a barrier to TPT implementation in LMICs, TPT is systematically recommended in PWH in all settings with high incidence for TB regardless of TST or IGRAs results once TB is ruled out [16]. In high income countries TPT is recommended only in patients with positive IGRA or TST, particularly in those with lower CD4 counts [17,102,103].

ART is also strongly associated with a reduction in the incidence of tuberculosis and before universal ART was recommended, delaying ART until CD4 dropped below 200/mm³ resulted in a persistent increased risk of TB [104–106]. The benefits of TPT for PWH with high CD4 counts also have been demonstrated in the TEMPRANO trial showing the reduction of both TB incidence and overall mortality [107–109]. In countries with low TB incidence, the benefits of TPT are difficult to assess in randomized trials but in cohorts the benefits of TPT was found in patients with positive TST or IGRAs with a number needed to treat > 20 to avoid one case of TB [110–112].

In LMICs, less than 30% of PWH received TPT treatment in 2020, despite proven efficacy and the WHO recommendation to start TPT at HIV infection diagnosis a decade ago [1]. Coverage varies widely among countries: a few high burden countries account for two thirds of TPT provision and report a median TPT coverage around 50% of the targeted population [1,60]. Barriers to TPT with isoniazid are the duration of treatment (at least six months) and the potential adherence issues. Also, efficacy of isoniazid alone may be lower than when used in association with a rifamycin. Shorter weekly 3HP or daily 1HP regimens had high efficacy in randomized trials and are now recommended by the WHO [113,114]. However, access to rifapentine is limited in LMICs and it may take years to transition from IPT to 3HP or 1HP. In high income countries, extensive screening for active TB in patients with CD4 counts below 200/mm³ is easier with access to chest CT scan or invasive procedures as tissue biopsies. Access to bacteriological labs infrastructure also improves TB diagnosis and the monitoring of patients is more frequent, allowing to re-test for TB in case of evocative symptoms. The prescription of TPT is heterogeneous in Europe and in the US with a low rate of TPT use [115,116].

2.5 Empirical treatment of tuberculosis

Systematic TB treatment of severely immunocompromised PWH without evidence of TB was also evaluated. The objective was to reduce TB-related mortality during the first year on ART in PWH with CD4 counts $<100/\text{mm}^3$. The REMEMBER trial compared systematic TB treatment versus IPT in patients with CD4 counts $<100/\text{mm}^3$ also receiving ART and not suspected to have active TB. Death rates were overall low and similar between arms [113]. In the ANRS 12290 STATIS trial, empirical TB treatment was compared with a test-guided initiation of TB treatment, i.e., systematic testing for TB using chest X ray and Xpert® MTB/RIF in sputum. The patients did not receive IPT in the STATIS study. There was also no benefits on mortality and high rates of TB treatment toxicity were seen in this study [114]. These two trials confirm that both extensive screening for TB in PWH with low CD4 counts and IPT provision were effective measures to reduce TB related mortality in regions with high incidence of TB.

3 Antiretroviral therapy in people with HIV and tuberculosis

3.1 First-line antiretroviral therapy for the treatment of HIV infection

The benefits of ART in terms of HIV and non-HIV related morbidity and mortality, as well as prevention of HIV transmission have been largely demonstrated over the past 20 years [117–122]. It is now recommended to start ART in all PWH regardless of CD4 T cell counts both to prevent morbidity and mortality, but also as part of the treatment as prevention strategy (TasP) to reduce HIV acquisition [123,124]. Until 2009 only PWH with CD4-T cell-counts < 200/mm³ were eligible to ART, with a conditional recommendation to start in patients with less than 350/mm³ between 2006 and 2009 in some situations. It was only in 2013 that it was recommended to start ART in all PWH with CD4 counts < 500/mm³ and the WHO recommended universal treatment regardless of CD4 T cell counts in 2015, three years after European and US guidelines (figure 3) [102,124–127].

Figure 3 : Evolution of CD4-count criteria for starting antiretroviral therapy in asymptomatic persons with HIV infection, according to different guidelines (DHHS, EACS, IAS, WHO) [102,124–127].

CD4/mm ³	Guidelines	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
>500	US (DHHS)																		
	European (EACS)																		
	IAS																		
	WHO																		
350-500	US (DHHS)																		
	European (EACS)																		
	IAS																		
	WHO																		
200-349	US (DHHS)																		
	European (EACS)																		
	IAS																		
	WHO																		
<200	US (DHHS)																		
	European (EACS)																		
	IAS																		
	WHO																		

Since 1996 the use of combined ART (cART) with three active drugs combining two NRTIs and a third agent remains the preferred option for initial ART. The type of NRTIs backbone and third agent have changed over the years towards better tolerated combinations that could be used in all PWH, including pregnant women, and those with hepatitis B or TB co-infection. Regimens have also evolved dramatically from multiple pills that needed to be taken twice or thrice daily with food, resulting in high pill burden, to once daily multiple pill regimens. The availability of single tablet regimens with fixed dose combinations of the three drugs was a further step to treatment simplification. The number of drugs available also increased substantially in high income countries and more than 30 drugs have been approved for the treatment of HIV infection, allowing to personalise treatment when necessary

(appendix 5). Access to all the drugs available is limited in LMICs and the options to personalise treatment are limited.

Current ART regimens for treatment-naive patients consist of two NRTIs in combination with a third active drug from one of the following classes: INSTI, NNRTI, or a PI with a pharmacokinetic booster (either cobicistat or ritonavir). The preferred options for NRTI backbone are tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) in combination with lamivudine (3TC) or emtricitabine (FTC). All international guidelines recommend to use an INSTI as the preferred third agent, with NNRTIs and boosted PIs as alternatives in special situations (table 1).

Table 1 : Latest guidelines for preferred and recommended initial antiretroviral therapy for people with HIV.

	EACS 2021 [102]	DHHS 2022 [127]	IAS-USA 2020 [128]	WHO 2022 [123]
Preferred options*	Bictegravir+ TAF/FTC Dolutegravir+ TAF/FTC Dolutegravir+ TDF/XTC	Bictegravir+ TAF/FTC Dolutegravir+ TAF/FTC Dolutegravir+ TDF/XTC	Bictegravir+ TAF/FTC Dolutegravir+ TAF/FTC Dolutegravir+ TDF/XTC	Dolutegravir + TDF/3TC
Other recommended options*	Dolutegravir + ABC/3TC Dolutegravir + 3TC Raltegravir+ TAF/FTC Raltegravir+ TDF/XTC Doravirine+TDF/3TC	Dolutegravir + ABC/3TC	Dolutegravir + 3TC	

*as single tablet fixed dose combination or not. ABC: abacavir, TAF: tenofovir alafenamide, TDF: tenofovir disoproxil fumarate, 3TC: lamivudine, FTC : emtricitabine, XTC: lamivudine or emtricitabine

In LMICs, dolutegravir is recommended for all PWH starting ART since 2018, and national programs also have progressively switched all virologically suppressed patients that were on efavirenz to dolutegravir. In the specific context of PWH treated for tuberculosis, the WHO also recommends to use dolutegravir and to double the dose to take into account the interaction with rifampicin (see below) [123].

3.2 Drug intolerance in the context of HIV-infection and tuberculosis co-treatment

The frequency of treatment-related adverse events has been reported to be higher in PWH treated for TB, often leading to tuberculosis treatment or ART interruptions. ART and TB drugs share common side effects, especially hepatotoxicity and allergy. One other contributing factor is the frequency of other

comedications, especially cotrimoxazole prophylaxis which is also frequently responsible for drug induced allergy. In the initial period of highly active ART introduction in London, Dean *et al.* reported adverse events in more than 50% of patients treated for both HIV and TB, about twice the rate reported in patients treated only for TB [129]. Most common adverse events were gastro-intestinal, rash and peripheral neuropathy. The majority of patients was on stavudine and or didanosine at the time, well known to cause neuropathy [129]. In REMoxTB trial PWH receiving standard TB therapy had higher risk of grade 3 or 4 adverse events (AE): one or more grade 3 or 4 AE considered to be at least possibly related to treatment was reported by 11 of 42 (26.2%) PWH and 14 of 220 (6.4%) people without HIV [130].

In randomised clinical trials evaluating the introduction of ART during TB treatment (integrated ART) compared to delaying ART introduction until after the end of TB treatment, there was no difference in severe adverse events between participants on ART and those not on ART, indicating that concomitant ART and TB treatment administration did not increase the risk of drug related adverse events [131,132]. However, in the STATIS trial evaluating empirical TB treatment, grade 3 or 4 drug-related adverse events were higher with systematic treatment (17.4% vs. 7.2%) and the events were mostly hepatotoxicity and rash [114]. The discrepancies between studies may be related to other co-factors that are difficult to assess, as different genetic backgrounds or co-medications.

The management of adverse events in the context of HIV/TB co-infection is difficult because it is hard to determine the causative drug and decide the best schedule for reintroduction of both TB drugs and ART. The potential severity of hepatotoxicity is also one other concern. Although rare, fulminant hepatitis is a complication feared by all clinicians who treat patients for TB because TB drugs, especially isoniazid and pyrazinamide are known to cause liver failure and may lead to liver transplantation [133].

3.3 Pharmacokinetics of rifampicin and interactions with antiretroviral therapy

All four anti-TB drugs used in the standard combination have excellent bioavailability and maximum concentrations are reached within 1 to 3 hours after drug intake. For isoniazid and rifampicin, food can reduce absorption (up to 30% reduction in rifampicin peak concentration), leading to the recommendation to take all TB drugs on a fasting state [48]. There is a very important inter-individual variability in TB drugs exposure. This has been studied particularly for rifampicin and isoniazid. Different genetic polymorphisms of transporters or enzymes involved in drugs metabolism have been associated to lower drugs concentrations [134,135]. Pharmacokinetic studies have shown that in PWH peak concentrations and exposure to all four first line TB drugs were lower than expected for full efficacy in PWH compared to healthy volunteers, especially for rifampicin and pyrazinamide [92,136]. PWH may also have other conditions that influence drug absorption as comedications and

gastrointestinal diseases (chronic diarrhoea, HIV related enteropathy...) [48,136,137]. Tuberculosis itself may also impair the intestinal absorption of TB drugs [135].

Rifampicin activates the transcription of genes involved in the metabolism of many drugs and induces cytochrome P 450 (CYP), UDP-glucuronosyltransferase (UGT) 1A1 and efflux transporter P-glycoprotein also known as multidrug resistance protein 1 (MDR-1), among others [48]. These metabolic pathways are involved in the metabolism of most antiretroviral drugs, especially CYP3A4 and CYP2B6 (table 2). The steady state of rifampicin induction is reached after approximately two weeks and upon rifampicin discontinuation, it takes three to four weeks for the induction effect to end.

In the context of HIV and TB co-infection, suboptimal exposure to TB drugs may result in a higher risk of treatment failure or relapse which is a concern particularly in severely ill PWH. Some studies reported that rifampicin exposure was highly reduced in but the doses used were not always weight adjusted [48]. When standard dose of rifampicin was used and was weight adjusted, rifampicin concentrations seemed adequate [48].

The benefits of using higher doses of rifampicin may be particularly relevant in PWH. The results of an ongoing trial in Uganda showed that 89% of PWH treated with oral standard dose rifampicin (10 mg/kg/day) had sub-therapeutic rifampicin concentration in cerebro-spinal fluid (CSF) whereas >90% of patients on high-dose oral (35 mg/kg/d) or intravenous (20 mg/kg/d) rifampicin had CSF rifampicin levels above MICs [138]. Other trials are ongoing to evaluate TB treatment outcomes using high doses of rifampicin in PWH with TB meningitis or other severe forms of tuberculosis (Intense TBM NCT04145258, Datura NCT04738812).

The clinical benefits of therapeutic drug monitoring of TB drugs and the correlation between some PK parameters and clinical outcomes as mortality or relapse are difficult to demonstrate. A recent meta-analysis showed that a high number of patients (with or without HIV) had peak concentrations of TB drugs below the accepted targets for efficacy but clinical outcomes were not affected by low TB drugs dosages [139]. The real-life experience shows that TB treatment outcomes are fairly good all over the world without drug monitoring or dose adjustment [1].

Hepatic CYP3A4 and CYP2B6 are major metabolic pathways for PIs, NNRTIs and also the second-generation INSTIs. Therefore, the metabolism of these three classes of antiretroviral drugs is affected by rifampicin induction of cytochromes.

Boosted PIs cannot be administered together with rifampicin because PIs are substrate of hepatic cytochromes and the PK enhancers are potent inhibitors of CYP3A4.

The metabolism of NRTIs is not affected by rifampicin but the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF) is transported via the transporter P-glycoprotein. TAF drug levels are

reduced when co-administered with rifampicin but the interaction does not seem to affect intracellular concentrations and antiviral efficacy [140–142].

The interaction between rifampicin and the NNRTI efavirenz, results in a modest reduction of efavirenz levels but this has no impact on virologic efficacy as demonstrated in several PK studies or randomised trials comparing efavirenz- and nevirapine-based ART in different settings [143–148]. Based on those results efavirenz became the drug of choice for the treatment of PWH with tuberculosis. There is an important interindividual variability in efavirenz PK parameters but doses might need adjustment only in special circumstances, particularly high body weight [148]. Genetic factors as CYP2B6 polymorphisms have been associated with increased efavirenz concentrations and toxicity [148,149]. Isoniazid also increases efavirenz dosages in patients with CYP2B6 polymorphisms [150].

Another NNRTI, nevirapine was evaluated in PWH treated for TB (see 3.4). PK studies showed that the interaction with rifampicin results in suboptimal plasmatic levels of nevirapine during the lead-in phase (200 mg daily for the first 2 weeks of therapy before using the standard 200 mg twice daily dose) but this was corrected when treatment was started directly with 200 mg twice daily [151].

A summary of drug-drug interactions between rifampicin and the most frequently used antiretrovirals is presented in table 2.

3.4 Trials evaluating antiretroviral therapy efficacy in people with HIV and TB conducted before the availability of INSTIs

Virologic efficacy of ART in the context of tuberculosis co-treatment has been evaluated in clinical trials. The largest phase III non-inferiority randomised clinical trial evaluating two different NNRTIs based ART in the context of TB was the ANRS 12146 ANRS 12146 CARINEMO trial [146]. This study was conducted in Mozambique between 2007 and 2010 and enrolled 570 participants that were randomised to receive an efavirenz based regimen or a nevirapine based regimen (twice daily, using the lead-in dose). The primary endpoint was HIV-1 RNA <50 copies per mL at W48 (patients who died or were lost to follow-up before week 48 were considered as treatment failures). Non inferiority of nevirapine to efavirenz was not shown, with 199/285 (64.6%) participants on nevirapine and 184/285 (68.9%) participants on efavirenz achieving an HIV RNA<50 copies/mL [146]. One other non-inferiority trial conducted in India before the ANRS 12146 CARINEMO study showed that nevirapine given once daily was inferior to efavirenz and the trial was interrupted by the IDMC. Two other trials with a smaller sample size also evaluated efavirenz compared to nevirapine [144,145]. Table 3 reports the results of randomised trials evaluating virologic efficacy of ART in the context of TB treatment.

Other trials evaluating the effects of ART on mortality, AIDS or TB related endpoints, reported the efficacy of ART as secondary endpoints, mostly efavirenz based regimens (table 4). These trials were

not face to face comparisons of different ART regimens and virologic endpoints were different from one trial to another but globally, 70-80% of virologic success rates were seen on efavirenz based regimens except in trials with high mortality [131,132,143,147,152–155].

Table 2: Antiretroviral drugs exposure when co-administered with rifampicin (for main first or second line ART drugs available in LMICs) (Adapted from Mentjes *et al.* [137] and www.hiv-druginteractions.org)

ARV drug	AUC change	Metabolism pathway	Studies evaluating virologic efficacy in PWH receiving rifampicin	Management of interaction
INSTI				
Raltegravir	↓40%	UGT1A1	Phase II non comparative study Phase III study	Standard 400 mg twice daily dose had similar efficacy that 800 mg twice daily
Dolutegravir	↓54%	UGT1A1, UGT1A3, UGT1A9 CYP3A4 P-glycoprotein BCRP	Phase II non comparative study	Double dolutegravir dose to 50 mg twice daily
Bictegravir (*alone or **combined with TAF/FTC)	↓75%* ↓61%**	UGT1A1 CYP3A4 P-glycoprotein	None	Not recommended with either rifampicin and rifabutin
Cabotegravir	↓60%	UGT1A1 CYP3A4 P-glycoprotein	None	Not recommended with either rifampicin and rifabutin (although modest 23% AUC reduction with rifabutin)
NNRTI				
Efavirenz	↓26%	CYP2B6 CYP3A4	Phase II and Phase III studies	No dose adjustment
Nevirapine	↓58%	CYP2B6 CYP3A4	Phase II and Phase III studies	Switch to rifabutin 300 mg daily
Etravirine	Expected to ↓	CYP3A4 CYP2C9 CYP2C19	None (2 case reports)	Interaction with rifamycins not studied Not recommended with either rifampicin and rifabutin

ARV drug	AUC change	Metabolism pathway	Studies evaluating virologic efficacy in PWH receiving rifampicin	Management of interaction
Rilpivirine	↓80%	CYP3A4	None	Switch to rifabutin 300 mg daily and double rilpivirine dose
Doravirine	↓88%	CYP3A4	None	Switch to rifabutin 300 mg daily and double doravirine dose
Nucleotide RTI				
Tenofovir alafenamide	↓54%	P-glycoprotein BCRP OATP1B1	Phase 2	Standard dose (higher intracellular drug than TDF suggesting that dose adjustment is unnecessary)
Ritonavir boosted protease inhibitors				
Atazanavir/r	↓72%	CYP3A4 P-glycoprotein	3 case reports	Switch to rifabutin 150 mg daily
Lopinavir/r	↓75%	CYP3A4 P-glycoprotein	Phase II	Switch to rifabutin 150 mg daily or Double dose
Darunavir/r	↓57%	CYP3A4 P-glycoprotein	Phase II	Switch to rifabutin 150 mg daily

AUC: Area under the curve, INSTI integrase strand transfer inhibitor, NNRTI non-nucleoside reverse transcriptase inhibitor; /r : ritonavir (booster); BCRP : breast cancer resistance protein (transporter); OATP1B1 : organic anion-transporting polypeptide 1B1. TAF/FTC : tenofovir alafenamide/emtricitabine

Table 3: Randomised clinical trials evaluating ART efficacy as primary outcome in PWH receiving rifampicin to treat TB

	Country Intervention Enrolment period	Type of trial/number of participants (n)	ART (third agent)	Primary end-point	CD4 at baseline median /mm³	Median HIV RNA at baseline log₁₀ copies/mL	Virologic outcome
Bonnet <i>et al.</i> [146]	Mozambique 2007-2010 2 ART strategies	Phase III open label randomised Non inferiority trial (10% margin) n=570	EFV 600 mg qd vs NVP 200 mg bid	HIV-1 RNA <50 cp/mL at W48 (ITT and PP)	86-92	5.5-5.7	HIV RNA<50 cp/mL ITT : EFV 184/285 (68.9%) NVP 199/285 (64.6%) OT : EFV 194/246 (78.9%) NVP 170/243 (70%)
Manosuthi <i>et al.</i>[144]	Thailand 2006-2007 2 ART strategies and PK study	Phase III, open label randomised powered to detect a 20% difference n=142	EFV 600 mg qd vs NVP 200 mg bid	HIV-1 RNA <50 cp/mL at W48 (ITT and PP) Drug dosages	55-74	5.75	HIV RNA<50 cp/mL ITT : EFV 52/71 (73.2%) NVP 51/71 (71.8%) OT : EFV 52/62 (83.9%) NVP 51/55 (92.7%)
Swaminathan <i>et al</i> [145].	India 2 ART strategies	Phase III open label randomised Non inferiority trial (15% margin), sample size 180 n= 116*	EFV 600 mg qd vs NVP 400 mg qd	Unfavorable outcome at W24 (ITT) (Death or HIV-1 RNA ≥400 copies/mL, default, or termination of study drug as a result of toxicity)	83-85	5.4-5.5	HIV RNA<400 cp/mL ITT EFV 50/59 (85%) NVP 37/57 (65%)

	Country Intervention Enrolment period	Type of trial/number of participants (n)	ART (third agent)	Primary end-point	CD4 at baseline median /mm ³	Median HIV RNA at baseline log ₁₀ copies/mL	Virologic outcome
Grinsztejn <i>et al.</i>[156]	France Brazil 3 ART strategies	Phase II open label randomised n=153 France n=8 Brazil n=145	RAL 400mg bid RAL800 mg bid EFV 600 mg qd	HIV RNA <50 copies per mL at W24 (mITT)	140	4,9	HIV RNA<50 cp/mL EFV 32/51 (63%) RAL400 39/51 (76%) RAL800 40/51 (78%) <u>Secondary endpoint :</u> HIV RNA <50 copies per mL at W48 (snapshot): EFV 37/51 (73%) RAL400 39/51 (76%) RAL800 32/51 (63%)
Dooley <i>et al.</i>[157]	2015-2017 Argentina Brazil Mexico Peru Russia South Africa Thailand 2 ART strategies	Phase II, open label randomised non-comparative n=113	DTG 50 mg bid EFV 600 mg qd	HIV RNA <50 copies per mL at W48 (snapshot)	208	5.10-5.24	HIV RNA<50 cp/mL EFV 36/44 (82%) DTG 52/69 (75%)
Griesel <i>et al.</i>[158]	2019-2022 South-Africa 2 ART strategies	Phase II placebo controlled randomised , non-comparative n=108	DTG 50 mg bid DTG 50 mg qd	HIV RNA <50 copies per mL at W24 (snapshot)	197 DTG 50 mg bid 183 DTG 50 mg qd	5.1-5.2	HIV RNA<50 cp/mL DTG 50 mg bid 43/52 (83%) DTG 50 mg qd 44/53 (83%)

*Interim analysis: trial stopped for futility

qd *quo die*: once daily; bid *bis in die*: twice daily. EFV efavirenz, ABC abacavir, NVP: nevirapine, DTG: dolutegravir, RAL: raltegravir

Table 4 : Virological outcomes in randomized clinical trials evaluating pharmacokinetics of antiretrovirals or timing of ART introduction with virologic outcomes as secondary endpoints in PWH receiving rifampicin as part of TB treatment (not powered for comparisons).

	Country Intervention Enrolment period	Type of trial/number of participants	ART §	Primary end-point	Secondary virological endpoint	Median CD4 at baseline / mm ³	Median HIV RNA at baseline log ₁₀ cp/mL	Virological outcomes	endpoint
NNRTIs									
Manosuthi et al.[143]	Thailand 2003-2004 PK study	Phase II, open label randomised N=84	EFV 600 mg vs EFV 800 mg	EFV dosages at W24	HIV RNA<50 cp/mL at W48	32-37.5	5.5 -5.6	EFV 600 mg: 31/42 (74.0%) EFV 800 mg: 27/42 (64.0%)	
Manosuthi et al.	Thailand 2006-2007 PK study	Phase II, open label randomised N=142	EFV 600 mg vs NVP	EFV and NVP dosages at W24			5.8	EFV 34/140 (24.2%) vs NVP 30/144(20.8%)	
Sinha et al.[147]	India 2007-2013 Effect of 2 ART regimens on mortality	Phase III, open label randomised N=284	EFV 600 mg vs NVP	Deaths and/or ART failure at W96	Virological failure (HIV RNA≥400 cp/mL up to W96)	127-133	5.3- 5.5	EFV 34/140 (24.2%) vs NVP 30/144(20.8%)	
Abdool Karim et al.[159]	South Africa 2005-2008 Early or delayed ART	Phase III, open label randomized N=642	EFV 600 mg	death from any cause at W 96	HIV RNA<50 cp/mL 6 months after ART initiation and 12 months post-randomization	140-150	5.2	<u>M6 ART</u> 213/236 (86.0%) <u>M12 from rando.</u> 269/311 (86.4%)	
Blanc et al.[152]	Cambodia 2006-2007 Early or delayed ART	Phase III, open label randomised N=661	EFV 600 mg	death from any cause at W50	Undetectable HIV RNA at W50 (threshold?)	25	5.64	Participants who started ART and alive at W50 with undetectable HIV RNA: 96% (in the overall population 203/661 (30.8%))	

	Country Intervention Enrolment period	Type of trial/number of participants	ART §	Primary end-point	Secondary virological endpoint	Median CD4 at baseline / mm ³	Median HIV RNA at baseline log ₁₀ cp/mL	Virological endpoint outcomes
Havir <i>et al.</i>[153]	Africa (69%), Asia (6%), North America (5%), South America (20%) 2006-2009 Early or delayed ART	Phase III, open label randomised N=809	EFV 600 mg	AIDS or death at W48	HIV RNA<400 cp/mL at W48	77	5.43	Participants who started ART and alive at W48 with HIV RNA<400 cp/mL: 594/663 (89,5%) (in the overall population 594/809 (73,4%))
Mfinanga <i>et al.</i>[131]	South Africa (6%), Tanzania (29%), Uganda (30%), Zambia (35%) 2008-2013 Early or delayed ART	Phase III, open label randomised N=1538	EFV 600 mg	Death, failure of TB treatment or TB recurrence at 12 months	No virologic outcome	367	NA	NA
Manosuthi <i>et al</i> [154]	Thailand Early or delayed ART 2009-2011	Phase III, open label randomised N=156	EFV 600 mg	Death from any cause at 1 year	No virologic outcome	38-53	5.71-5.83	NA
Shao <i>et al.</i>[155]	Tanzania 2004-2005 Early or delayed ART	Phase III, open label randomised N=70	ABC§§	Safety of triple NRTIs and TB IRIS	HIV RNA <400 cp/mL and < 50cp/mL at 104 weeks or ART	103	NA	Overall, 81% of participants with HIV RNA<400 cp/mL and 70% with HIV RNA < 50cp/mL at W104
Boosted PIs								
Kendall <i>et al.</i>[160]	Brazil (40%), Peru (8%), Haiti (25%), Kenya (13%), and South Africa (14%) 2013-2016 PK study	Phase II, open label randomised initially designed to compare 3 arms with sample size 470 powered to detect 20% difference but only 70 participants enrolled	Arm B: LPV/r 800 mg/200 mg BID <i>Arms A and C : LPV/r 400 mg/100 mg BID+ Rifabutin+/- raltegravir 400 mg bid)</i>	PK study at W 12	HIV RNA< 400 cp/mL at week 48	130	4.6	<i>Arm A: 11/24 (46%) Arm B: 13/24 (54%) Arm C :13/23 (57%)</i>

EFV efavirenz, ABC abacavir, NVP: nevirapine, LPV/r: ritonavir boosted lopinavir. PK: pharmacokinetic.§ Combination of 2 NRTIs and a third drug§§triple NRTIs combination zidovudine+lamivudine+ abacavir

qd *quo die*: once daily; bid *bis in die*: twice daily

3.5 Rifabutin: an alternative to rifampicin

Rifabutin is another rifamycin that was used for the prevention of *Mycobacterium avium complex* (MAC) disease in the early days of the AIDS epidemic. Rifabutin has low activity on extracellular bacilli meaning it has low early bactericidal activity. It is however, very active on intracellular bacilli and has thus good sterilizing activity [30]. Rifabutin has lower interaction potential than rifampicin as it has weak induction properties and can be co-administered with boosted PIs. It is metabolized by CYP3A and the dose of rifabutin needs to be reduced by 50 to 75% when co-administered with PK enhancers ritonavir and cobicistat [161,162]. Current US and European guidelines recommend using rifabutin at the dose of 150 mg daily when patients are receiving a boosted PI regimen [102,163].

No large non-inferiority clinical trial has compared rifabutin and rifampicin efficacy in PWH treated for tuberculosis. A meta-analysis showed that rifabutin was effective and safe in combination with PIs and that it could be cost-effective compared to using super-boosted lopinavir but the studies included in the meta-analysis combined small randomised clinical trials and cohort studies, in both people with and without HIV. The criteria used most frequently to evaluate efficacy was sputum conversion which is not adapted to PWH who often have smear negative TB [164]. Importantly, rifabutin is not available in most countries with a high TB burden.

3.6 Best timing of antiretroviral therapy to reduce mortality in people with HIV and tuberculosis

Early introduction of ART is recommended in case of opportunistic infection to reduce mortality since the early 2000's, at the exception of tuberculous meningitis and cryptococcal meningoencephalitis [31,102,124,127] ART introduction also reduces AIDS defining illness or death in PWH treated for tuberculosis [129,165]. Despite the risk of adverse events and of immune reconstitution inflammatory syndrome (IRIS), there is now strong evidence to support early introduction of ART in HIV infected ART-naïve patients with tuberculosis.

The SAPIT trial showed that introducing ART during TB treatment, compared to after TB treatment discontinuation reduced mortality by 56% [132]. This trial, along with the Camelia and Stride randomised clinical trials also showed that initiating ART during the intensive phase (first 2-4 weeks) of TB treatment rather than during the continuation phase (8-12 weeks) reduced AIDS related events and mortality [152,153,159]. The trial settings and the degree of immunosuppression differed but AIDS related events and/or mortality were reduced by 11% to 38% in severely immunocompromised patients. In the CAMELIA trial, mortality in patients with CD4 T-cell counts $<50/\text{mm}^3$, was reduced by 38% in those initiating ART 2 weeks after starting TB treatment as compared to those who initiated ART 8 weeks after TB treatment initiation [152]. The results of these studies were key to shape the WHO

recommendation to start ART 2 weeks after antituberculosis treatment initiation in patients with CD4 counts $< 50/\text{mm}^3$. The benefits in patients with CD4 counts $\geq 200/\text{mm}^3$ were not demonstrated in these trials, nor in the TB-HAART trial [131]. Consequently, ART could be delayed in such patients but no later than 8 weeks after the beginning of TB treatment [131,132,153,166]. More recently, this recommendation was changed in the era of universal treatment and it is now recommended to initiate ART within 2 weeks of antituberculosis therapy in all PWH with tuberculosis regardless of CD4 counts, except for TB meningitis. In this situation, ART should be started four weeks after TB treatment initiation) [102,123,127,167].

3.7 Immune restoration inflammatory syndrome

Paradoxical worsening of TB related lesions following TB treatment initiation was reported since the first TB treatments in the 1950's with the description of fever and worsening of lymphadenopathies or cerebral tuberculomas in children [168,169]. In the AIDS epidemic, when combined ART was introduced, immune reconstitution inflammatory syndrome (IRIS) was described more frequently for tuberculosis and also for other opportunistic infections [170,171]. The frequency of TB-IRIS was found to be approximately of 15 to 18% in two meta-analysis overall, with higher proportions in patient with CD4 counts $< 50 \text{ mm}^3$ at ART initiation and with high TB bacterial loads [172,173]. The diagnosis of IRIS is difficult to confirm in the absence of a validated diagnostic test and requires to exclude TB treatment failure, other infections or drug intolerance which can be difficult in resource limited settings. An international definition of IRIS was adopted to limit heterogeneity in case definitions among studies [171].

IRIS underlying immunological mechanisms include restoration of innate immune specific responses to *M. tuberculosis*, mediated by interferon- γ (IFN- γ) and tumor necrosis factor (TNF) combined with the failure to control the inflammatory response [68,137,174]. The clinical consequences are rarely fatal but severe forms can result in hospitalizations or may require procedures to relieve compressive lesions. Steroids are used to treat the most severe forms of IRIS and case reports have highlighted the efficacy of TNF-inhibitors in steroid dependent cases [175,176]. One trial conducted in South Africa showed that 4 weeks of steroids prevented IRIS with approximately 30% reduction of IRIS related symptoms, especially fever or radiological worsening, but there were no survival benefits [177]. Adjunctive steroids are systematically recommended in TB meningitis although the benefits on mortality in PWH has not been proved to date [178–180]. The results of the ACT HIV trial evaluated systematic steroids in TB meningitis in PWH are pending and will provide important data on this question (NCT03092817).

4 Integrase inhibitors: a new opportunity to treat HIV-infection in the context of TB

Before 2018 and the availability of dolutegravir in HIV programs in LMICS, efavirenz was the preferred first-line treatment in LMICs and the alternatives for second line therapy were protease inhibitors [181]. In case of efavirenz intolerance or resistance, alternatives were scarce and protease inhibitors (double boosted lopinavir was then recommended with rifampicin) were prone to drug-drug interactions which left people infected with TB with virtually no alternative in countries where rifabutin was not available. In many instances people would continue TB treatment without ART, with a high risk of TB treatment failure, relapse, reinfection, or development of other opportunistic infections and death.

Efavirenz-based regimens were not always optimal for the treatment of PWH with TB. Efavirenz can be poorly tolerated in some individuals because of neurosensory adverse events and rashes that can be difficult to distinguish from rashes related to TB treatment. In case of primary or acquired resistance to NNRTIs mutations, efavirenz cannot be used and efavirenz was also suspected to be at risk of teratogenicity, even if its data are conflicting on that matter [182–185]. For all these reasons, alternatives to efavirenz-based regimens were sought to treat patients co-infected with HIV and TB.

4.1 Raltegravir

Raltegravir is one of the first-generation INSTIs and was the first drug of this family to be developed. In the pivotal phase III STARTMRK trial, at week 48 raltegravir was shown to be non-inferior to efavirenz in ART naïve PWH, with virologic efficacy rates of 86.1% and 81.9% on raltegravir and efavirenz respectively, and raltegravir was better tolerated [186].

Raltegravir is metabolized by UGT1A1 mediated glucuronidation and is not metabolized via the hepatic cytochromes. However, rifampicin is also an inducer of UGT1A1 and raltegravir has significant pharmacokinetic interaction with rifampicin. In 10 healthy volunteers, a pharmacokinetic (PK) study after administration of a single dose of raltegravir 400mg with or without rifampicin showed lower raltegravir plasma concentrations and exposure in the presence of rifampicin, with a 40% decrease in area under the curve (AUC), 38% decrease in C_{max} and a 60% decrease in trough concentrations (C_{12h}) [187]. Doubling raltegravir dose compensated for the effect of rifampicin on raltegravir exposure but did not overcome the reduction of trough concentrations that remained 53% lower than expected [187]. These results have led to recommend to double the dose and use raltegravir at a dosage of 800 mg twice daily in combination with rifampicin. However, there were no clinical data to support this recommendation and the safety of high doses of raltegravir in patients receiving TB treatment was not known. Interestingly, in phase 1 dosing studies in healthy volunteers, raltegravir doses from 100 to 1600

mg twice daily resulted in trough concentrations above the 95% inhibitory concentration (IC₉₅) of 33 nM [188]. This was confirmed in PWH, using doses from 100, 200, 400, and 600 mg twice daily and short-term monotherapy provided the same antiviral efficacy at all doses [189]. In a phase II study comparing the 48-week antiviral efficacy of the same dosages, 85% to 98% and 83% to 88% of patients achieved HIV RNA <50 copies in the raltegravir 100, 200, 400, and 600 mg groups, respectively. Raltegravir AUC_{0-12h}, C_{max}, and C_{12h} were 30 to 40% higher when raltegravir was co-administered with tenofovir and lamivudine, related to a modest interaction with tenofovir [190].

Altogether, these data suggested that a reduction of raltegravir doses in the presence of rifampicin might have little or no impact on virologic efficacy of raltegravir when used in combination with tenofovir and lamivudine. This was the rationale to evaluate raltegravir at standard or double dose for the treatment of PWH treated with rifampicin for tuberculosis.

The Reflate TB trial was a multicentre, open-label, randomised, phase II trial with 51 patients per arm, conducted in Brazil and in France, where ART-naïve PWH were randomised to receive raltegravir (400 or 800 mg twice daily) or efavirenz (600 mg once daily), in combination with tenofovir and lamivudine (300 mg once daily), after starting rifampicin-based TB treatment. After the end of TB treatment including rifampicin, the raltegravir dose was reduced to 400 mg twice daily in the higher dose arm. In this phase II trial, at week 24, virologic success rates (HIV RNA <50 copies/mL) were 78%, 76% and 63% in the raltegravir 800, raltegravir 400, and efavirenz arms, respectively. At week 48, success rates were 63%, 76% and 67% in the raltegravir 800, raltegravir 400, and efavirenz arms, respectively with a similar number of virologic failures [156].

Safety of the three regimens was good with one, one, and three grade 3/4 ALT elevations in the raltegravir 800, raltegravir 400 and efavirenz arms, respectively up to week 48. However, more patients in the raltegravir high dose arm had to discontinue ART because of an adverse event, and one patient developed fulminant hepatitis and underwent liver transplant. TB treatment success rates were 90%, 90% and 88% in the raltegravir 800, raltegravir 400 and efavirenz arms, respectively [156].

The Reflate TB PK sub-study assessed drug-drug interactions between raltegravir and rifampicin. Patients in both raltegravir arms (21 with raltegravir 400 mg and 16 with raltegravir 800 mg) had PK performed with and without rifampicin. In the higher dose arm, a third PK was performed after raltegravir was reduced to 400 mg twice daily. There was a huge variability of raltegravir pharmacokinetic parameters and a trend toward lower concentrations when raltegravir 400 mg twice daily was combined with rifampicin which was partially compensated by the 800 mg twice daily dosing (table 4) [191]. In the raltegravir 400 group, there was a reduction in C_{12h} (geometric mean ratio, (GMR) 69%) but AUC was similar (GMR 96%) in the presence of rifampicin, meaning that the interaction seemed lower than what was observed in healthy volunteers, probably because other drugs were involved and also because raltegravir was taken with food in the trial. We concluded that raltegravir could be

administered without regards to food but in PK studies conducted in healthy volunteers, administration of raltegravir following a high-fat meal increased raltegravir AUC and C_{max} by approximately 2- fold and a 4-fold increase in C_{12h} [192].

Table 4: Comparison of plasma Raltegravir pharmacokinetics following administration of raltegravir 400 mg twice daily (arm 1) with and without rifampicin (adapted from Taburet *et al. Clin Infect Dis* 2015 [191]).

PK parameter	Period 1 (on RIF) Geometric mean, Median (Range)	Period 2 (off RIF) Geometric mean, Median (Range)	Period 1/period 2 GMR (90%CI)	P Value
C_{max} , ng/mL	2929 3322 (228-7920)	2966 3572 (184-11 632)	0.99 (0.67-1.45)	0.18
T_{max} , h 4 (0-12) 2 (0-8)
C_0 , ng/mL	165 205 (5-4395)	368 414 (10-2065)	0.46	0.96
C_{12} , ng/mL	128 142 (10-1642)	199 260 (24-5732)	0.69 (0.42-1.13)	0.69
AUC ₀₋₁₂ , ng x h/mL	9278 10 300 (740- 21 835)	9910 14814 (672- 34 437)	0.94 (0.64-1.37)	0.24

PK : pharmacokinetic, RIF : rifampicin, GMR : geometric mean ratio, C_{max} : peak concentration, T_{max} : time to peak concentration, C_0 concentration before administration and C_{12} : concentration 12 hours post-drug intake, AUC₀₋₁₂: area under the curve 0 to 12 h post dose

4.2 Dolutegravir

The second generation INSTI Dolutegravir, was shown to be non-inferior to efavirenz with better safety profile [193,194]. It was also shown to be non-inferior to raltegravir, with the advantage of once daily dosing [195].

Dolutegravir has high genetic barrier for the selection of resistance which explains why emergence of drug resistance is rare [196]. Compared to raltegravir it has a once daily dosing and was developed as co-formulated with different NRTI backbones in single tablet regimens. Moreover, it is less prone to drug-drug interactions than the drugs that need to be given with PK enhancers as it is the case for elvitegravir, a first generation INSTI or PIs. Tolerance was also good overall in the pivotal studies [193,195]. All these reasons prompted the WHO to recommend dolutegravir based regimens for all PWH including those treated for TB since 2018. Since then, national programs organized their transition

from efavirenz based regimens to dolutegravir based regimens [124]. In PWH with tuberculosis treated with rifampicin, the dose needs to be doubled which requires a twice daily drug intake.

As raltegravir, dolutegravir is mainly metabolized by UGT1A1 but CYP3A is also a metabolic pathway for this drug. Consequently, rifampicin induces dolutegravir metabolism and results in lower dolutegravir AUC, C_{max} and C_{12h} concentrations. In healthy volunteers, AUC of dolutegravir was reduced by 60% when co-administered with rifampicin but doubling dolutegravir dose maintained dolutegravir exposure similar to that of standard dolutegravir dose without rifampicin [197].

The INSPIRING non-comparative, open-label, randomised trial evaluated dolutegravir 50 mg twice daily and efavirenz 600 mg once daily in adult PWH with TB. PWH treated with rifampicin were randomised to receive either efavirenz or a double dose dolutegravir during the first 24 weeks and then the standard dose of dolutegravir up to week 48 [157]. Participants with $CD4$ counts $<50/mm^3$, with central nervous system, miliary, pericardial TB or chronic hepatitis B were not eligible. The median $CD4$ counts and HIV-1 RNA were $208/mm^3$ and $5.10 \log_{10}$ copies/mL in the dolutegravir arm, and $202/mm^3$ and $5.2 \log_{10}$ copies/mL in the efavirenz arm, respectively. Almost all participants had pulmonary, pleural or mediastinal tuberculosis. The rates of viral suppression were similar between the two groups, 75% (52/69) and 82% (36/44) in the dolutegravir and efavirenz arms, respectively [157].

One other phase II randomised placebo-controlled trial, the RADIANT trial, evaluated the PK and W24 efficacy of the standard or double dose of dolutegravir in the presence of rifampicin in 108 individuals. The results of the Week 24 efficacy results were presented earlier this year [158]. A similar proportion of participants, 83% in both arms, achieved virologic suppression at week 24. Importantly, ART related pill burden was the same in both groups because in the dolutegravir standard dose arm, participants also received a placebo of the additional dolutegravir pill [158]. A similar study, but with an open label design, is ongoing in Thailand and plans to enrol 200 patients and evaluate dolutegravir PK parameters and W48 efficacy of the two dolutegravir dosages. The interim analysis of the first 40 participants showed a 60% reduction of AUC as expected but with apparently no impact on virologic control as 90% of the participants in both arms had HIV-1 RNA below 50 copies/mL at W 48 [198].

Given the lack of data from phase III, randomised trials, it is important to look at data from national or international cohorts in real life and programmatic settings. During the early period of dolutegravir roll-out within the national program in Botswana, 90% of the 739 patients taking dolutegravir 50 mg twice or once daily and treated concomitantly with rifampicin, achieved HIV RNA <400 copies/mL at week 12 or 24 [199]. However, it is important to note that more than 70% of the patients were already virologically suppressed when they started TB treatment [199]. A recent survey conducted within the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium, showed that 96% of the 90 participating sites located in 18 African countries has transitioned to dolutegravir to treat PWH with TB [200]. Among patients with at least one viral load measure available within the first year of follow-

up, the cumulative incidence of virologic suppression was 274/465 (58.9%) in patients receiving dolutegravir and 348/702 (49.6%) in those receiving efavirenz during the same period. The virologic endpoint was defined as the earliest documentation of HIV RNA measurement <1,000 copies/mL during the 12 months following TB diagnosis, which is not a usual measure of virologic suppression [200].

To date, no larger phase 3 trial was performed to confirm that dolutegravir-based ART was non-inferior to an efavirenz-based regimen and it is unlikely that one will be conducted in the context of dolutegravir roll out since 2018. Indeed, the WHO recommends to use dolutegravir in PWH with TB based on the results from the INSPIRING trial and the limited data that are available from national programs [124]. As more and more PWH with TB receive dolutegravir, countries need to improve monitoring of these patients and release their surveillance.

4.3 Other INSTIs

Elvitegravir is a first generation INSTI that need to be administered with a PK enhancer. It is co-formulated with cobicistat and TAF/FTC as single tablet regimen [201]. Consequently, boosted elvitegravir cannot be administered with rifampicin.

The INSTIs Bictegravir and cabotegravir, were developed after dolutegravir [202,203]. Bictegravir is co-formulated with TAF/FTC and this combination is available in high income countries as a single tablet. Co-formulated Bictegravir/TAF/FTC was non inferior to co-formulated dolutegravir, abacavir, and lamivudine, with 92% of virologic success at week 48 with both regimens [204]. Cabotegravir is a long acting INSTI that allows bimonthly administration together with injectable rilpivirine and has recently been approved for the treatment of PWH with sustained virologic control as switch therapy [202]. It has also been approved as pre-exposure prophylaxis (PrEP) regimen and some LMICs may start to use it as PrEP in the next few years [205,206].

Both bictegravir and cabotegravir have a favourable profile regarding drug-drug interactions as they are metabolized mainly by UGT1A1. Both are also metabolized by CYP3A4, and P-glycoprotein 1; their metabolism is thus also induced by rifampicin. As for raltegravir and dolutegravir, doubling the dose of bictegravir compensates the interaction with rifampicin in healthy volunteers; a phase II trial is ongoing to compare the use of double dose bictegravir to double dose dolutegravir in the context of TB treatment with rifampicin (INSIGHT study NCT04734652). There are no data regarding long acting injectable cabotegravir when co-administered with rifampicin but a PK study conducted in healthy volunteers taking a single dose of the oral formulation of cabotegravir showed a 59% reduction of cabotegravir AUC following rifampicin induction [207]. Whether rifampicin has an effect on the injectable formulation is not known.

5 The Reflate TB2 trial: testing raltegravir as an alternative to efavirenz

Following the Reflate TB trial that showed raltegravir at the usual dose of 400 twice daily provided good efficacy and safety in PWH with TB, the results needed to be confirmed in a phase III trial to determine if raltegravir would be suitable alternative to efavirenz.

The Reflate TB 2 trial started being implemented in 2013 and the first patients were enrolled in 2015, before dolutegravir became the first-line option as per the WHO guidelines. The trial was conducted during the same period than the INSPIRING study evaluating two doses of dolutegravir in PWH treated for tuberculosis [157].

The Reflate TB 2 trial was the first large international phase III randomised trial evaluating an integrase inhibitor-based ART regimen in the context of HIV/TB co-infection. Data from larger studies will not be available soon, therefore the results are important to assess integrase inhibitors-based ART in PWH with TB. The ANRS research network provided the possibility to conduct an international trial to address the question of new ARV strategies in countries with a high number of TB in PWH.

Mozambique, Vietnam, and Brazil are in the list of the 30 countries with high TB burden, and Côte d'Ivoire is also considered as high burden country for tuberculosis. In 2012, when the reflate TB 2 trial was designed, the World Health Organization (WHO) reported an annual TB incidence rate of 548, 199, 191, and 42 per 100,000 inhabitants, in Mozambique, Vietnam, Brazil and Côte d'Ivoire, respectively, and an incidence of HIV-associated TB of 347, 16, 50 and 8.2 per 100,000 inhabitants, respectively.

5.1 Study design

This was a phase III, multicentre, open-label, randomised non-inferiority trial to compare the efficacy and safety of two different first-line treatment strategies in ART naïve HIV-1 infected patients diagnosed with TB, regardless of CD4 T-cell counts, over 48 weeks: tenofovir + lamivudine + raltegravir and tenofovir + lamivudine + efavirenz. The trial was implemented in five countries: Brazil, Côte d'Ivoire, France, Mozambique and Vietnam. The final list of countries and sites participating to the trial will be validated by the sponsor before the beginning of the trial.

ART-naïve PWH with active TB disease receiving a standard rifampicin-based antituberculosis treatment were included in the trial and randomised between 2 arms: the raltegravir 400 mg twice daily arm or the efavirenz 600 mg once daily arm, each in combination with tenofovir and lamivudine.

All participants received a rifampicin-based TB regimen according to World Health Organization (WHO) and national treatment guidelines. Rifampicin-based TB treatment had to be started ≤ 8 weeks before inclusion and ART initiation.

Patients were followed for 48 weeks after entry in the trial (ART initiation).

The aim of the phase III trial was not to further explore the interaction between rifampicin and raltegravir but rather to validate that raltegravir would be a valid alternative to efavirenz in PWH with TB who could not receive efavirenz. Regarding the choice of the timepoint chosen to measure the main endpoint, it seemed more robust to evaluate antiviral efficacy at week 48 rather than week 24, for comparability with trials evaluating ART. Moreover, at week 48 the participants would be off TB treatment, including those for whom the duration of TB treatment could exceed 6 months, in case of bone or joint tuberculosis. Secondly, a primary endpoint at week 24 may favour the raltegravir arm as virologic response is well known to be slower with efavirenz. Finally, this was first trial evaluating raltegravir in resource limited countries in ART naïve PWH and these results would provide very useful information in hope for the future availability of raltegravir.

5.2 Primary endpoint

The primary endpoint was the proportion of patients in virologic success at week 48. Virologic success was defined as plasma HIV-1 RNA below 50 copies/mL at week 48 with a window period of 42 to 54 weeks (FDA snapshot algorithm [208]). If HIV-1 RNA was not available at W48 visit, the closest HIV-1 RNA measurement in the window period was used.

The following events were considered as failures:

- Plasma HIV-1 RNA level ≥ 50 copies/mL at week 48
- Discontinuation of the trial strategy before week 48.
Permanent discontinuations of raltegravir or efavirenz (due to adverse events or other reasons) were considered as strategy discontinuations. Discontinuations of tenofovir or lamivudine were not considered as strategy discontinuations, provided these drugs were replaced with other NRTIs.
- Missing plasma HIV-1 RNA at week 48
- Discontinuation of the trial before week 48 due to loss to follow-up, death, transfer out, withdrawal of consent

5.3 Study population

5.3.1 Inclusion criteria

- Signed informed consent form
- Aged 18 years or more
- Confirmed HIV-1 infection as documented at any time prior to trial entry per national HIV testing procedures
- ART naïve
- For women of childbearing potential i.e. women of childbearing age who are not menopausal, or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) or not refraining from sexual activity: negative urinary test for pregnancy and acceptance to use contraceptive methods
- Confirmed or probable active TB disease of any location, except neurological (meningitis or encephalitis), according to the following criteria based on WHO updated definitions:
- Bacteriologically confirmed pulmonary or extrapulmonary TB, e.g., TB with a biological specimen positive by smear microscopy, culture or nucleic acid amplification test (such as Xpert MTB/RIF).
- Clinically diagnosed pulmonary or extrapulmonary TB with:
 - o Typical histological evidence of TB (caseous or granulomatous) on biopsy specimen or positive urinary LAM test
- OR
- o A significant improvement on TB treatment
- Ongoing standard rifampicin-containing TB treatment for ≤ 8 weeks at inclusion
- For French patients, affiliation to a Social Security program (State Medical Aid or Aide Médical d'Etat)
- There were no inclusion criteria based on CD4 T-cell count.

5.3.2 Non-inclusion criteria

- HIV-2 co-infection
- Impaired hepatic function (icterus or ALT (SGPT) > 5 ULN)
- Haemoglobin < 6.5 g/dl
- Creatinine clearance < 60 ml/min (assessed by the Cockcroft and Gault formula)
- *Mycobacterium tuberculosis* strain resistant to rifampicin (current or past).

Xpert MTB/RIF, line probe assays or culture with DST could be used to assess resistance to rifampicin. Probable cases of TB without drug-resistance data could be included.

- Neurological TB (meningitis or encephalitis)
- Severe associated diseases requiring specific treatment (including all specific AIDS defining illnesses other than TB, and any severe sepsis)
- Any condition which might, in the investigator's opinion, compromise the safety of treatment and/or patient's adherence to trial procedures including very severe TB-related clinical condition
- Concomitant treatments including phenytoin or phenobarbital (compounds interacting with UGT1A1)
- For HCV co-infected patients, need to start specific treatment for hepatitis during the trial duration
 - For women of childbearing potential: pregnancy or breastfeeding, refusal to use a contraceptive method, any history of ARV intake for prevention of mother to child transmission of HIV
- Subjects participating in another clinical trial evaluating therapies and including an exclusion period that is still in force during the screening phase
- Person under guardianship, or deprived of freedom by a judicial or administrative decision

5.4 Study settings

Trial sites chosen to participate to the Reflate TB 2 trial were located in countries considered as high TB burden or high TB incidence by the WHO (Brazil, Côte d'Ivoire, Mozambique, and Vietnam). They were all linked to an ANRS|MIE research site or had previously participated in ANRS|MIE funded clinical trials.

All sites had laboratory facilities meeting the requirements for the trial in terms of bacteriology, virology, biobanking facilities. All had participated to previous ANRS|MIE funded researches on TB/HIV co-infection: ANRS 12180 Reflate TB in Brazil, ANRS 12136 Temprano in Côte d'Ivoire, and ANRS 12150 RAP, ANRS 12229 PAANTHER 01, and ANRS 12290 STATIS in Vietnam. In Mozambique, the research team collaborated to the ANRS12146 CARINEMO trial. In France, Saint Louis Hospital, Paris, was involved in the phase II ANRS 12180 Reflate TB trial, and the ANRS 129 BKVIR study was also a trial site.

There were 6 sites located in 5 countries:

- INI/FIOCRUZ in Rio de Janeiro, Brazil

- Centre de Prise en Charge de Recherche et de Formation, CePreF-Aconda-VS, Abidjan, Côte d'Ivoire
- Dermatology and Infectious diseases department CHU de Treichville in Abidjan, Côte d'Ivoire
- Infectious Diseases Department, Saint-Louis hospital, in Paris, France
- Machava hospital in Maputo, Mozambique
- Pham Ngoc Thach hospital in Ho Chi Minh City, Vietnam

5.5 Study procedures

Eligible subjects were randomised in a 1:1 ratio for a total of 230 patients per trial arm, using a computer-generated random list. The randomization list was established by the trial statistician prior to the start of the trial and kept secret from the investigators. Randomization was blocked and stratified by country. The number of participants per stratum was not capped. The investigators had 24/24h private access to the online randomization system, which allowed them to check the eligibility criteria, confirm the decision to randomize, and sequentially allocate a trial arm to the patient.

5.6 Personal implication

I have been involved in trials dealing with HIV/TB co-infection for 15 years. It started by a meeting with the Brazilian Ministry of Health and Pr Beatriz Grinzstejn to discuss research priorities for Brazil and we then co-designed the ANRS 12180 Replate TB trial. As the principal investigator of a previous study, the ANRS 138 Easier trial, I had worked on raltegravir PK. This trial evaluated the switch from enfuvirtide to raltegravir in highly pre-treated PWH and included a PK sub-study. Following the discussion with Brazilian colleagues, we developed a phase II randomised clinical trial to evaluate raltegravir as an alternative to efavirenz for ART in PWH with tuberculosis. I served as the French co-coordinating investigator with Pr Jean-Michel Molina, who was the French coordinating investigator and Pr Beatriz Grinsztejn, the Brazilian coordinating investigator. I presented the study results at the AIDS 2012 conference in Washington and contributed to the main publication that was later released in the *Lancet Infectious Diseases* [209].

As we felt that a phase III study was needed to confirm that raltegravir at standard doses would be an alternative to efavirenz, we discussed with other teams within the ANRS network to include a wider representation of PWH with TB and set a multi-site, multi-continent trial. We submitted the project to the ANRS for funding with teams from the University of Bordeaux, Brazil, Côte D'Ivoire, Mozambique and Vietnam, and it was accepted for funding in 2013. As the French coordinating investigator, I participated in and coordinated all the steps of the study implementation: writing the initial proposal and

later the final protocol, in close cooperation with Dr Olivier Marcy who was then the international manager of the study and Pr Beatriz Grinsztejn. I also contributed to write up study procedures and statistical analysis plan, and participated to the opening of study sites. I worked with the project manager and statistician to prepare and present the data for all scientific and DSMB meetings. Finally, I worked closely with the trial statistician, Corine Chazallon, as well as with Olivier Marcy and Beatriz Grinsztejn to set up the secondary analysis and then worked on the review of the data, analyses, interpretation of the results and manuscript writing. Inclusions in the ANRS 12300 Reflate TB 2 trial lasted from September 2015 to January 2018 and the follow-up of the participants ended in December 2018. I presented the results of the primary end-point analysis at the AIDS 2019 conference in Mexico.

Following the study results and with the support of both Olivier Marcy and Beatriz Grinsztejn, I decided to start a PhD in epidemiology to strengthen my research skills. The PhD objective was to further analyse the Reflate TB2 trial results and notably to try to understand our negative findings. We were surprised by the discrepancies between the phase II and the phase III studies and also by the fact that in the Reflate TB 2 trial, there were no differences between the two arms during the first 24 weeks of the trial the period when the interaction with rifampicin might have been a problem. We felt that we needed to consider adherence issues and also try to understand why the results were different in Brazil compared to other countries. These questions were addressed in this thesis as I will present the secondary analysis from the Reflate TB 2 trial and also the pooled analysis of the Reflate TB and Reflate TB2 studies.

I continued to work as a clinician during these years and decided to continue doing so during my PhD but the COVID-19 epidemic irrupted in our lives and interfered with my research activities. We were however able to conclude the analysis we had planned with some delay so I finally decided to take one year off the clinic to finalize the writing of the papers and set up the next study on ART in PWH treated for TB using real life data within the Brazilian HIV and TB programs.

6 Thesis objectives

The main objective of this thesis was to assess whether a raltegravir-based regimen could be used as an alternative to the previously (before 2018) WHO-recommended efavirenz-based regimen for antiretroviral treatment of HIV-infected adults with tuberculosis.

The following three specific objectives were defined:

- To assess the non-inferiority of a raltegravir containing regimen as compared to an efavirenz based regimen in terms of virologic efficacy at 48 weeks in ART-naïve PWH treated for active TB, and to compare both regimens in terms of tolerance. The analysis of the determinants of virologic success and adherence were included in this specific objective in order to better understand the trial results.
- To assess the impact of the country of origin and other determinants on virologic success rates at 48 weeks of raltegravir and efavirenz-containing regimens, respectively, among ART naïve PWH treated for active tuberculosis in Brazil, Côte d'Ivoire, Mozambique, and Vietnam. This objective would be achieved by merging the data from the phase 2 study Reflate TB and the phase 3 study Reflate TB2.
- To evaluate the virologic efficacy of raltegravir, dolutegravir and efavirenz containing regimens in a programmatic environment, by analysing the data from the national Brazilian HIV program.

Due to the irruption of the COVID-19 pandemic, the last specific objective could not be concluded but the study was started in 2022 and analysis are ongoing.

7 Non-inferiority of raltegravir versus efavirenz (Reflate TB2 trial)

7.1 Research question and background

As its virologic efficacy is not affected by the interaction with rifampicin, efavirenz has been the drug of choice for many years to treat PWH with TB. Tolerance issues and transmitted NNRTI-resistance has prompted the search for alternatives to efavirenz-based regimens in LMICs, particularly for the treatment of PWH also treated for TB. Following encouraging results from the phase II ANRS 12180 Reflate TB trial, we designed the phase III ANRS 12300 Reflate TB 2 trial with the objective of confirming that raltegravir at a standard dose of 400 mg twice daily could be used to treat PWH with TB and could represent an alternative to efavirenz, the recommended treatment at the time.

Another INSTI, dolutegravir, is now the preferred option for first line treatment of people with HIV and TB. The WHO recommendation issued on July 2018 is based on the results from the INSPIRING trial, a non-comparative randomised trial presented in March 2018 at the Conference on Retroviruses and Opportunistic Infections (CROI 2018) and published in 2020. Indeed, to our knowledge, the Reflate TB 2 study is the only phase III comparative randomised clinical trial assessing the efficacy of an INSTI-based antiretroviral regimen in the context of HIV and tuberculosis co-infection. Data from large randomised studies will not be available soon, therefore the results of the Reflate TB 2 study are important to evaluate INSTI-based ART, especially in the context of dolutegravir roll-out.

7.2 De Castro *et al. Lancet Infectious Diseases* 2021; 21:813-22.

The results of the ANRS Reflate TB trial that enrolled 460 participants were presented at the 19th international AIDS conference, Washington DC 22-27 July 2012 and was then published in the *Lancet Infectious Diseases* in 2021. The supplementary appendix published with the article is presented in appendix 6. The editorial by A. Pozniak and G. Meintjes published in the same issue of the *Lancet ID* is presented in appendix 7.

Standard dose raltegravir or efavirenz-based antiretroviral treatment for patients co-infected with HIV and tuberculosis (ANRS 12 300 Replate TB 2): an open-label, non-inferiority, randomised, phase 3 trial



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Summary

Background In patients co-infected with HIV and tuberculosis, antiretroviral therapy options are limited due to drug—drug interactions with rifampicin. A previous phase 2 trial indicated that raltegravir 400 mg twice a day or efavirenz 600 mg once a day might have similar virological efficacy in patients given rifampicin. In this phase 3 trial, we assessed the non-inferiority of raltegravir to efavirenz.

Methods We did a multicentre, open-label, non-inferiority, randomised, phase 3 trial at six sites in Côte d'Ivoire, Brazil, France, Mozambique, and Vietnam. We included antiretroviral therapy (ART)-naive adults (aged ≥ 18 years) with confirmed HIV-1 infection and bacteriologically confirmed or clinically diagnosed tuberculosis who had initiated rifampicin-containing tuberculosis treatment within the past 8 weeks. Using computerised random numbers, we randomly assigned participants (1:1; stratified by country) to receive raltegravir 400 mg twice daily or efavirenz 600 mg once daily, both in combination with tenofovir and lamivudine. The primary outcome was the proportion of patients with virological suppression at week 48 (defined as plasma HIV RNA concentration < 50 copies per mL). The prespecified non-inferiority margin was 12%. The primary outcome was assessed in the intention-to-treat population, which included all randomly assigned patients (excluding two patients with HIV-2 infection and one patient with HIV-1 RNA concentration of < 50 copies per mL at inclusion), and the on-treatment population, which included all patients in the intention-to-treat population who initiated treatment and were continuing allocated treatment at week 48, and patients who had discontinued allocated treatment due to death or virological failure. Safety was assessed in all patients who received at least one dose of the assigned treatment regimen. This study is registered with ClinicalTrials.gov, NCT02273765.

Findings Between Sept 28, 2015, and Jan 5, 2018, 460 participants were randomly assigned to raltegravir (n=230) or efavirenz (n=230), of whom 457 patients (230 patients in the raltegravir group; 227 patients in the efavirenz group) were included in the intention-to-treat analysis and 410 (206 patients in the raltegravir group; 204 patients in the efavirenz group) in the on-treatment analysis. At baseline, the median CD4 count was 103 cells per μL and median plasma HIV RNA concentration was $5.5 \log_{10}$ copies per mL (IQR 5.0–5.8). 310 (68%) of 457 participants had bacteriologically-confirmed tuberculosis. In the intention-to-treat population, at week 48, 140 (61%) of 230 participants in the raltegravir group and 150 (66%) of 227 patients in the efavirenz had achieved virological suppression (between-group difference -5.2% [95% CI -14.0 to 3.6]), thus raltegravir did not meet the predefined criterion for non-inferiority. The most frequent adverse events were HIV-associated non-AIDS illnesses (eight [3%] of 229 patients in the raltegravir group; 21 [9%] of 230 patients in the efavirenz group) and AIDS-defining illnesses (ten [4%] patients in the raltegravir group; 13 [6%] patients in the efavirenz group). 58 (25%) of 229 patients in raltegravir group and 66 (29%) of 230 patients in the efavirenz group had grade 3 or 4 adverse events. 26 (6%) of 457 patients died during follow-up: 14 in the efavirenz group and 12 in the raltegravir group.

Interpretation In patients with HIV given tuberculosis treatment, non-inferiority of raltegravir compared with efavirenz was not shown. Raltegravir was well tolerated and could be considered as an option, but only in selected patients.

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Introduction

Tuberculosis remains a major cause of morbidity and mortality in patients with HIV, with 815 000 cases

and 208 000 deaths worldwide reported in 2019.^{1,2} In antiretroviral therapy (ART)-naive adults co-infected with HIV and tuberculosis, the initiation of ART can be

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For the French translation of the abstract see Online for appendix 2

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See Online for appendix 3

Research in context

Evidence before this study

The interaction between antiretroviral drugs and rifampicin restricts antiretroviral therapy (ART) treatment options for patients with HIV receiving tuberculosis treatment. The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz is less affected by the interaction with rifampicin than protease inhibitors and has been the drug of choice for many years. Tolerance issues and transmitted NNRTIs-resistance has prompted the search for alternatives to efavirenz-based regimens to treat patients co-infected with HIV and *Mycobacterium tuberculosis*.

We searched PubMed for randomised controlled clinical trials published in English between Jan 1, 2010, and July 8, 2020, using the search terms (“tuberculosis” AND “raltegravir” AND “HIV”) OR (“tuberculosis” AND “integrase inhibitor” AND “HIV”). Our search yielded no comparative controlled trials, but identified two non-comparative randomised trials.

The National French Agency for AIDS Research (ANRS) 12180 Replate TB phase 2 trial compared raltegravir-based and efavirenz-based antiretroviral therapy in patients co-infected with HIV and tuberculosis treated with rifampicin, with raltegravir 400 mg twice daily or 800 mg twice daily during anti-tuberculosis treatment. In patients given raltegravir 400 mg twice daily, the interaction with rifampicin had a minimal impact on virological efficacy: patients given efavirenz 600 mg once daily, raltegravir 400 mg twice daily, or 800 mg twice daily had similar virological responses at week 24 and week 48. The reduction in pharmacokinetic parameters (area under the curve, maximum plasma concentration, and minimum plasma concentration) was lower than expected in the group given raltegravir 400 mg twice daily, and safety of the three regimens was tolerable and similar in the three groups. On the basis of these findings, we designed the Replate TB 2 open-label, comparative, non-inferiority, randomised phase 3 trial to confirm these results.

Another integrase inhibitor, dolutegravir, is now recommended by WHO as the preferred first-line ART and is replacing efavirenz in low-income and middle-income countries. For patients with tuberculosis, one non-comparative randomised study showed that virological response in patients given dolutegravir was similar to that of efavirenz in patients with pulmonary tuberculosis and CD4 counts higher than 50 cells per μL .

Added value of this study

To our knowledge, the Replate TB 2 study is the only comparative, randomised, phase 3 trial to assess the efficacy of an integrase inhibitor-based antiretroviral regimen in the context of HIV and tuberculosis co-infection. Despite promising results from the previous phase 2 study, at week 48, non-inferiority of raltegravir (400 mg twice daily) compared with efavirenz (600 mg once daily) was not shown. The proportion of participants who achieved virological suppression was lower than expected in both groups, especially in patients with high HIV RNA concentrations; adherence was also lower than expected in both groups after week 24, with a larger proportion of patients with poor adherence observed in the raltegravir group than the efavirenz group. No major safety issues were identified in either group.

Implications of all the available evidence

Although non-inferiority of raltegravir was not demonstrated, the Replate TB 2 study provides important data in the field of HIV and tuberculosis co-infection. Efavirenz should remain an option for ART in patients with HIV and tuberculosis co-infection. However, raltegravir 400 mg could be an acceptable alternative in selected patients. Our results also raise concerns about the use of twice daily dosing of integrase inhibitors regimens in the context of dolutegravir rollout in countries with a high tuberculosis burden.

challenging due to treatment-related adverse events, drug–drug interactions, and risk of immune reconstitution inflammatory syndrome, which can be difficult to manage.^{3–8}

Drug–drug interactions between antiretrovirals and rifampicin—the cornerstone of tuberculosis treatment and a potent inducer of cytochrome P450—restrict ART options in patients co-infected with HIV and tuberculosis. Many studies have shown that efavirenz is less affected by the interaction with rifampicin than other antiretrovirals, with good virological outcomes.^{9–13} However, treatment with efavirenz is not always possible due to neurological tolerance and transmitted drug-resistance.

Integrase inhibitors have a good safety profile and could represent an alternative to efavirenz in patients with tuberculosis. However, these inhibitors also have

significant drug–drug interaction with rifampicin. Dolutegravir, the preferred first-line antiretroviral in low-income and middle-income countries, is recommended at a double dose for patients with tuberculosis on the basis of pharmacokinetic data in healthy volunteers and on results of one non-comparative trial.^{14–16} Similarly, raltegravir is recommended at double doses on the basis of pharmacokinetic data in healthy volunteers.¹⁷

The results of the National French Agency for AIDS Research (ANRS) 12180 Replate TB phase 2 trial indicated that in patients with tuberculosis given raltegravir at a standard dose (400 mg twice daily), the interaction with rifampicin had minimal impact on virological efficacy.^{18,19} A similar proportion of patients given ART regimens containing efavirenz 600 mg once daily or raltegravir 400 mg twice daily achieved virological suppression at 24 and 48 weeks. Additionally,

the associated pharmacokinetic substudy showed only a modest reduction in raltegravir trough concentrations and area under the curve in the raltegravir 400 mg twice a day group when co-administered with rifampicin.^{18,19} On the basis of these preliminary results, we did this phase 3 trial to assess the non-inferiority of raltegravir 400 mg (twice daily) to efavirenz for ART-naïve patients with HIV and tuberculosis co-infection.

Methods

Study design and participants

We did a multicentre, open-label, non-inferiority, randomised, phase 3 trial at six clinical sites in five countries (Brazil, Côte d'Ivoire, France, Mozambique, and Vietnam).

We enrolled ART-naïve adults (aged ≥ 18 years) with confirmed HIV-1 infection and bacteriologically confirmed or clinically diagnosed tuberculosis who had initiated rifampicin-containing tuberculosis treatment within the past 8 weeks. We excluded patients with HIV-2 infection, tuberculous meningitis, rifampicin-resistant tuberculosis, impaired hepatic function (icterus or alanine aminotransferase concentrations greater than five times the upper limit of normal), creatinine clearance of less than 60 mL/min, haemoglobin concentration of less than 6.5 g/dL, and patients who were pregnant or breastfeeding. Full inclusion and exclusion criteria are listed in appendix 3 (p 4).

The study protocol (appendix 3 p 12) was approved by relevant national and local ethics committees in all participating countries. All participants provided signed informed consent before enrolment.

Randomisation and masking

We randomly assigned eligible participants (1:1) to receive raltegravir 400 mg twice a day (standard dose), or efavirenz 600 mg once daily, both in association with tenofovir disoproxil fumarate and lamivudine, using a computer-generated sequence. The trial statistician generated the randomisation list, using block randomisation (block size 4 or 6) stratified by country, before the beginning of the trial, using SAS software (version 9.4 M3). The randomisation list was kept confidential to site investigators who obtained automated treatment assignment centrally from the international coordinating clinical trial unit at INSERM U1219 (Bordeaux, France), via the electronic case report form. Patients and all investigators were unmasked to treatment assignment.

Procedures

All patients received a standard tuberculosis treatment regimen on a fasting state with isoniazid (4–6 mg/kg/day), rifampicin (8–12 mg/kg/day), pyrazinamide (20–30 mg/kg/day), and ethambutol (15–20 mg/kg/day) for 2 months (intensive phase), followed by isoniazid (4–6 mg/kg/day) and rifampicin (8–12 mg/kg/day) for 4 months (maintenance phase). In

case of skeletal or CNS tuberculosis, the duration of the maintenance phase could be extended and the total duration of tuberculosis treatment in the trial was left to the investigator's discretion.²⁰

As recommended by WHO,¹⁴ after 2–8 weeks of tuberculosis treatment (depending on CD4 cell counts), participants in the raltegravir group received 400 mg twice a day, tenofovir disoproxil fumarate 300 mg once daily, and lamivudine 300 mg once daily. Patients were instructed to take raltegravir with food to increase bioavailability. Patients in the efavirenz group received 600 mg once daily, tenofovir disoproxil fumarate 300 mg once daily, and lamivudine 300 mg once daily. The protocol allowed substitution of tenofovir and lamivudine with other nucleoside reverse-transcriptase inhibitors in case of intolerance. Tenofovir disoproxil fumarate, lamivudine, and efavirenz were provided by the National HIV/AIDS Programmes in Brazil, Côte d'Ivoire, Mozambique, and Vietnam and by the national health system in France. Raltegravir was donated by Merck. Co-trimoxazole prophylaxis was provided according to local recommendations (appendix 3 p 56).

We did clinical and laboratory assessments at all study visits (weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48; appendix 3 p 6).

Patients were diagnosed with confirmed or clinically diagnosed tuberculosis according to WHO guidelines,²¹ and started anti-tuberculosis treatment at clinics before referral to the trial site.

Smear microscopy, Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), and mycobacterial cultures on expectorated sputum and relevant extrapulmonary samples obtained at the time of tuberculosis diagnosis were collected, or done at the screening visit, if not already available. Chest radiographs were also done at the screening visit, unless already available at tuberculosis diagnosis. During follow-up, sputum smear microscopy and culture, and chest radiographs were done at baseline, week 8, and at the end of tuberculosis treatment. Hepatitis B (defined as detection of hepatitis B surface antigen), and hepatitis C (defined as detection of hepatitis C virus specific antibodies) infection status were assessed at the screening visit.

We measured plasma HIV-1 RNA concentrations at weeks 0, 4, 12, 24, 32, 40, and 48, using the COBAS Taqman HIV-1 assay (version 2.0; Roche Diagnostics, Meylan, France) in France, Côte d'Ivoire, Mozambique, and Vietnam, and the VERSANT HIV-RNA 3.0 assay (bDNA; Bayer, Berkeley, CA, USA) in Brazil.

Genotypic resistance mutations were assessed in patients with virological failure by sequencing the reverse transcriptase and integrase genes at the time of virological failure and at baseline, and reporting mutations as recommended by the ANRS AC43 Resistance Group.

We measured ART intake based on a pill count adherence ratio calculated over the 48 weeks of

For more on the recommendations of the ANRS AC43 Resistance Group see www.hivfrenchresistance.org

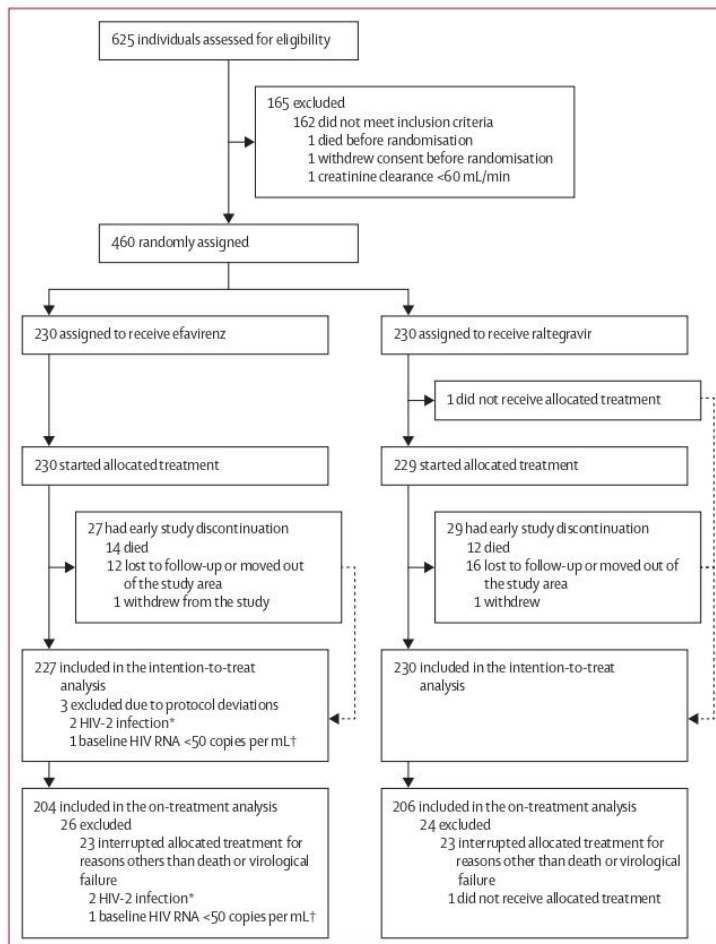


Figure 1: Study flow chart
*Same patients. †Same patients.

follow-up, as well as over the first and last 24 weeks (on and off anti-tuberculosis treatment).

Detailed procedures are provided in the protocol and statistical analysis plan (appendix 3 pp 13–144).

Outcomes

The primary outcome was the proportion of patients with virological suppression at week 48, defined as plasma HIV RNA concentration of less than 50 copies per mL on study drugs. This approach is consistent with the US Food and Drug Administration Snapshot algorithm.²² Permanent discontinuations of raltegravir or efavirenz were defined as virological non-response. Secondary endpoints were the proportion of patients with virological suppression at weeks 4, 12, 24, 32, 40 and 48 (with the same definition as the primary outcome), change in CD4 cell count from baseline at 48 weeks; proportion of patients with virological

failure (defined as confirmed plasma HIV RNA ≥ 200 copies per mL at 24 weeks, or rebounding above 200 copies per mL at any time in patients who had previously achieved viral suppression); emergence of genotypic resistance-associated mutations in patients with virological failure; occurrence of AIDS-defining events, HIV-associated non-AIDS-related severe illnesses, and grade 3 and 4 adverse events; tuberculosis treatment outcomes; frequency of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome; and adherence to ART. Pill count adherence ratio was calculated as the sum of the total number of pills given minus the total number of pills returned, divided by the total number of pills needed to cover the period. We defined poor adherence as a pill count adherence ratio of less than 95%.²²

The following secondary outcomes are not available yet, and will be reported elsewhere: time to death; time to adverse events; time to resistance; change in plasma HIV RNA concentrations from baseline to week 48; adherence to tuberculosis treatment; frequency, type, and time to immune reconstitution inflammatory syndrome; and non-tuberculosis associated immune reconstitution inflammatory syndrome.

Investigators recorded frequency, grade, and type of adverse events during the 48 weeks of the study in an unsolicited manner.

Statistical analysis

Assuming 70% of patients would achieve virological suppression at 48 weeks in both treatment groups, we estimated that a sample size of 230 participants in each group would provide 80% power to demonstrate non-inferiority at a one-sided α of 2.5%. Non-inferiority would be established if the lower bound of the 95% binomial CI for the treatment difference (raltegravir minus efavirenz) was greater than -12%. The primary non-inferiority analysis was done in the intention-to-treat population, which included all randomly assigned patients (excluding two patients with HIV-2 infection and one patient with a HIV-1 RNA concentration of <50 copies per mL at inclusion), and the on-treatment population, which included all patients in the intention-to-treat population who initiated treatment and were continuing allocated treatment at week 48, and patients who had discontinued allocated treatment due to death or virological failure. We did a sensitivity analysis stratified by country using logistic regression with a non-inferiority margin for the odds ratio of 0.592. Secondary endpoints were analysed in the intention-to-treat population, and safety was assessed in all patients who received at least one dose of the assigned treatment regimen. No interim analysis was planned, unless requested by the independent data monitoring committee.

We did a post-hoc analysis of virological suppression at 48 weeks using HIV-1 RNA thresholds of less than 200 and 1000 copies per mL. We did subgroup analyses of the differences in proportion of patients who met the

	Efavirenz (n=227)	Raltegravir (n=230)
Age, years	37 (30-43)	34 (28-42)
Sex		
Female	90 (40%)	92 (40%)
Male	137 (60%)	138 (60%)
Body-mass index, kg/m ² *	19.1 (17.5-20.8)	19.1 (17.6-21.2)
CD4 count, cells per μ L	108 (35-238)	99 (39-239)
≥ 200	154 (68%)	159 (69%)
≤ 50	77 (34%)	75 (33%)
Plasma HIV-1 RNA concentration, log ₁₀ copies per mL	5.5 (5.0-5.9)	5.5 (5.0-5.8)
≥ 100 000 copies per mL	165 (73%)	175/227 (77%)†
≥ 500 000 copies per mL	82 (36%)	75/227 (33%)†
Time since first HIV-positive test, days	22 (15-33)	21 (15-31)
Co-trimoxazole prophylaxis	201 (89%)	201 (87%)
Previous tuberculosis treatment	3 (1%)	3 (1%)
Anatomical site of tuberculosis disease		
Pulmonary only	159 (70%)	154 (67%)
Extrapulmonary only	43 (19%)	44 (19%)
Pulmonary and extrapulmonary	25 (11%)	32 (14%)
Bacteriologically confirmed tuberculosis‡	159 (70%)	151 (66%)
Smear microscopy positive for acid-fast bacilli	113 (50%)	95 (41%)
Xpert MTB/RIF test positive	132 (58%)	134 (58%)
Culture positive for mycobacterium tuberculosis	114 (50%)	114 (50%)
Probable (clinically diagnosed) tuberculosis‡	66 (29%)	76 (33%)
Urine lipoarabinomannan positive	18 (8%)	15 (7%)
Time on tuberculosis treatment at enrolment, days	20 (15-27)	20 (15-28)
Alanine aminotransferase concentration, IU/L	23 (15-37)	24 (15-38)
Creatinine clearance, mL/min per 1.73 m ²	98 (77-118)	103 (85-132)
Haemoglobin concentration, g/dL	9.9 (8.2-11.4)	9.8 (8.7-11.1)
Positive for hepatitis B virus surface antigen	21 (9%)	24 (10%)
Positive for hepatitis C virus antibodies	7 (3%)	2 (1%)

Data are n (%), median (IQR), or n/N (%). *Data were available for 226 participants in the efavirenz group and 227 participants in the raltegravir group. †HIV RNA data missing for three patients at baseline, however, all three patients had detectable HIV RNA at the first study visit (week 4), and thus were not excluded from the analysis. ‡According to WHO guidelines.²¹

Table 1: Baseline characteristics

primary endpoint by treatment stratified by baseline CD4 cell count, baseline HIV RNA, age, sex, body-mass index, and country. All statistical analysis were done using SAS software (version 9.4 M3). An independent data

	Efavirenz	Raltegravir	Difference (95% CI)*
Intention-to-treat population			
Patients assessed, n	227	230	NA
Virological suppression (HIV RNA <50 copies per mL)†	150 (66%)	140 (61%)	-5.2% (-14.0 to 3.6)
Virological non-response	51 (22%)	67 (29%)	..
HIV RNA ≥ 50 copies per mL	32 (14%)	46 (20%)	..
Discontinued due to lack of efficacy	9 (4%)	13 (6%)	..
Discontinued due to other reasons‡ and last available HIV RNA ≥ 50 copies per mL	10 (4%)	8 (3%)	..
No data in the 48-week window	26 (11%)	23 (10%)	..
Discontinued due to adverse events or death	18 (8%)	12 (5%)	..
Discontinued for other reasons	7 (3%)	11 (5%)	..
On study but missing data for 48-week window	1 (<1%)	0	..
On-treatment population			
Patients assessed, n	204	206	NA
Virological suppression (HIV RNA <50 copies per mL)†	150 (74%)	139 (67%)	-6.0% (-14.9 to 2.8)
Virological non-response	41 (20%)	58 (28%)	..
No data in 48-week window	13 (6%)	9 (4%)	..

Data are n or n (%). *95% binomial CI. †According to the US Federal Drug Administration.²² ‡Other reasons included discontinuation of study drug due to investigator's discretion, withdrawal of consent, loss to follow-up, noncompliance with study drug, protocol violation, or pregnancy.

Table 2: Primary endpoint at week 48

monitoring committee reviewed efficacy and safety data during the trial.

This study is registered with ClinicalTrials.gov, NCT02273765.

Role of the funding source

The study funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 28, 2015, and Jan 5, 2018, 460 participants were randomly assigned to raltegravir (n=230) or efavirenz (n=230), of whom 457 patients (230 patients in the raltegravir group, 227 patients in the efavirenz group) were included in the intention-to-treat analysis and 410 (206 patients in the raltegravir group, 204 patients in the efavirenz group) in the on-treatment analysis (figure 1). Overall, patient baseline characteristics were balanced between groups (table 1). The median CD4 count was 103 cells per μ L (IQR 38-239), the

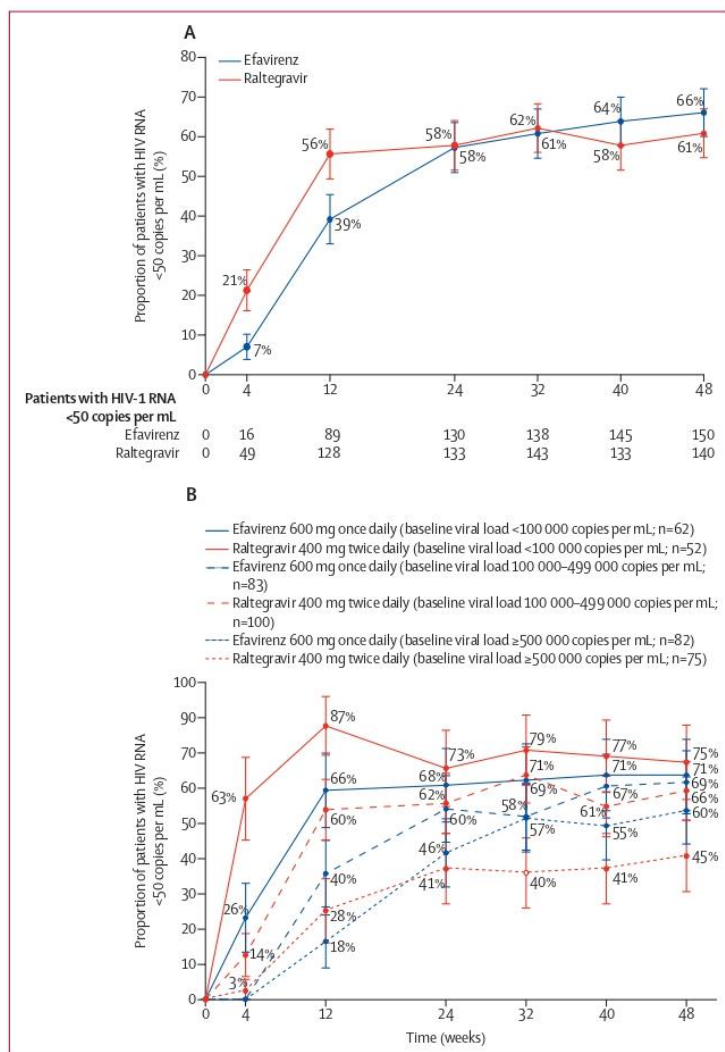


Figure 2: Viral suppression during 48-week follow-up overall (A) and by baseline viral load (B) in the intention-to-treat population (n=230 raltegravir group; n=227 efavirenz group). Error bars show 95% CI.

median plasma HIV RNA concentration was 5.5 log₁₀ copies per mL (5.0–5.8), and 157 (34%) of 457 patients had HIV RNA concentrations higher than 500 000 copies per mL. 310 (68%) of 457 participants had bacteriologically confirmed tuberculosis.

In the intention-to-treat analysis at week 48, 140 (61%) of 230 patients in the raltegravir group and 150 (66%) of 227 patients in the efavirenz group had achieved viral suppression (table 2). The difference in the proportion of patients who had achieved virological suppression at week 48 between the raltegravir and efavirenz groups was -5.2% (95% CI -14.0 to 3.6), thus raltegravir did not meet the pre-specified criterion for non-inferiority.

Non-inferiority was not demonstrated in the on-treatment analysis (between-group difference -6.0% [-14.9 to 2.8]; table 2) or sensitivity analyses stratified by country (appendix 3 p 7). The proportion of patients who had achieved virological suppression at week 48 did not differ by country, sex, age, body-mass index, CD4 cell count, or baseline HIV RNA concentration (appendix 3 p 8).

At 24 weeks, 133 (58%; 95% CI 51.4–64.2) of 230 patients in the raltegravir group and 130 (57%; 50.8–63.7) of 227 patients in the efavirenz group had achieved virological suppression on the allocated treatment (figure 2A). Overall, at 48 weeks, 83 (73%) of 114 patients with baseline HIV RNA concentrations of less than 100 000 copies per mL, 123 (67%) of 183 patients with HIV RNA concentrations of 100 000–499 000 copies per mL, and 83 (53%) of 157 patients with HIV RNA concentrations of 500 000 copies per mL or higher had achieved virological suppression. The proportion of patients who achieved virological suppression by baseline viral load in each group is shown in figure 2B.

In post-hoc analyses, at 48 weeks, 159 (69%; 95% CI 63–75) of 230 patients in the raltegravir group and 163 (72%; 66–78) of 227 patients in the efavirenz group had HIV RNA concentrations of less than 200 copies per mL, and 164 (71%; 65–77) of 230 patients in the raltegravir group and 166 (73%; 67–79) of 227 patients in the efavirenz group had HIV RNA concentrations of less than 1000 copies per mL.

75 patients met the definition of virological failure during follow-up: 42 (18%) of 230 patients in the raltegravir group and 33 (15%) of 227 patients in the efavirenz group. Of the 42 patients who had virological failure in the raltegravir group, amplification of the HIV-1 integrase gene was unsuccessful in ten (24%) patients and amplification of reverse transcriptase genes was unsuccessful in one (2%) patient. Of the 33 patients who had virological failure in the efavirenz group, amplification of integrase genes was unsuccessful in seven (21%) patients and amplification of reverse transcriptase genes was unsuccessful in one (3%) patient. In the raltegravir group, 26 (63%) of 41 patients had drug-associated mutations compared with 24 (75%) of 32 patients in the efavirenz group (appendix 3 p 9). Resistance to tenofovir was identified in two (5%) of 41 patients in the raltegravir group and 11 (34%) of 32 patients in the efavirenz group, resistance to raltegravir was identified in 12 (38%) of 32 patients in the raltegravir group, and resistance to efavirenz was identified in 22 (69%) of 32 patients in the efavirenz group. Dolutegravir remained active in eight of 12 patients with resistance to raltegravir.

The median increase in CD4 counts from baseline to week 48 was 183 cells per µL (IQR 106–276) in the raltegravir group and 172 cells per µL (100–258) in the efavirenz group.

The median pill count adherence ratio for the 48-week follow-up period was 96.9% (IQR 89.4–100.0) in the raltegravir group and 100.0% (94.3–104.5) in the

efavirenz group ($p < 0.0001$). Of the patients with available data, 96 (43%) of 224 patients in the raltegravir group and 60 (27%) of 222 patients in the efavirenz group had a pill count adherence ratio of less than 95% ($p < 0.0001$). The proportion of patients with poor adherence increased after week 24 in both treatment groups (table 3).

The median duration of tuberculosis treatment was 26 weeks (IQR 26–27) and did not differ between groups. Tuberculosis treatment success was achieved in 203 (89%) of 227 patients in the efavirenz group and 206 (91%) of 230 patients in the raltegravir group (appendix 3 p 11).

The proportion of patients with adverse events was similar between treatment groups (table 4). 21 (9%) of 230 patients in the efavirenz group and eight (3%) of 229 patients in the raltegravir group had HIV-associated non-AIDS illnesses. 13 (6%) of 230 patients in the efavirenz group and ten (4%) of 229 patients in the raltegravir group had AIDS-defining illnesses. Drug induced adverse events occurred in 30 (13%) of 230 patients in the efavirenz group and 25 (11%) of 229 patients in the raltegravir group. Nine (4%) of 230 patients in the efavirenz group and nine (4%) of 229 patients in the raltegravir group had hepatotoxicity, and seven (3%) of 230 patients in the efavirenz group had renal failure. Three (1%) of 230 patients in the efavirenz group and two (1%) of 229 patients in the raltegravir group permanently discontinued treatment due to adverse events. 26 (6%) of 457 patients died during follow-up: 14 in the efavirenz group and 12 in the raltegravir group. Most deaths (21 [81%] of 26) occurred within the first 24 weeks of the study (11 [42%] of 26 deaths occurred before week 8; ten [38%] of 26 deaths occurred between week 8 and week 24). Causes of death are in appendix 3 (p 12). 58 (25%) of 229 patients in the raltegravir group and 66 (29%) of 230 patients in the efavirenz group had grade 3 or 4 adverse events (table 4). Ten (4%) of 229 patients in the raltegravir group and 14 (6%) of 230 patients in the efavirenz group had grade 3 or 4 paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome.

Discussion

We did not demonstrate non-inferiority of a raltegravir 400 mg twice daily-based antiretroviral regimen compared with an efavirenz 600 mg once daily-based regimen in terms of virological suppression at week 48 in ART-naïve adults co-infected with HIV and tuberculosis. At week 48, 61% of patients in the raltegravir group and 66% of patients in the efavirenz group had achieved virological suppression (using a threshold of < 50 copies per mL), which was lower than we had hypothesised on the basis of previous studies of antiretroviral strategies in patients with tuberculosis.^{9,30}

To our knowledge, this is the first comparative, randomised phase 3 trial to date to compare an integrase inhibitor-based regimen with an efavirenz-based regimen in patients with HIV and tuberculosis co-infection in low-income and middle-income countries. In the

	Efavirenz	Raltegravir	p value
Week 0–48			
Patients with available data	222	224	..
Pill count adherence ratio	100.0% (94.3–104.5)	96.9% (89.4–100.0)	$p < 0.0001$
Pill count adherence ratio $< 95\%$	60 (27%)	96 (43%)	..
Week 0–24			
Patients with available data	222	223	..
Pill count adherence ratio	100.6% (95.2–103.0)	98.5% (92.7–100.3)	$p < 0.0001$
Pill count adherence ratio $< 95\%$	50 (23%)	74 (33%)	..
Week 24–48			
Patients with available data	199	210	..
Pill count adherence ratio	100.0% (93.7–106.5)	97.4% (84.0–100.9)	$p < 0.0001$
Pill count adherence ratio $< 95\%$	55 (28%)	87 (41%)	..

Data are n, median (IQR), or n (%).

Table 3: Pill count adherence ratio during the 48-week follow-up period

	Efavirenz (n=230)	Raltegravir (n=229)
AIDS-defining illnesses*	17; 13 (6%)	10; 10 (4%)
HIV-associated non-AIDS illnesses	24; 21 (9%)	9; 8 (3%)
Immune reconstitution inflammatory syndrome (grade 1–4)	39; 38 (17%)	26; 25 (11%)
Drug-induced adverse reactions (grade 1–4)	37; 30 (13%)	25; 25 (11%)
Leading to allocated treatment permanent discontinuation	3; 3 (1%)	2; 2 (1%)
Type of drug-induced adverse reaction		
Hepatotoxicity†	9; 9 (4%)	9; 9 (4%)
Hypersensitivity	2; 2 (1%)	1; 1 ($< 1\%$)
Renal failure	7; 7 (3%)	0
Rash	2; 1 ($< 1\%$)	0
Grade 3 and 4 events adverse events		
Immune reconstitution inflammatory syndrome	14; 14 (6%)	10; 10 (4%)
Drug-induced adverse reactions	26; 22 (10%)	24; 24 (10%)
Other	35; 30 (13%)	24; 24 (10%)
Median weight gain at week 48, kg (IQR)	7 (3–11)	9 (6–14)

Data are number of events; number of patients with at least one event (%), unless otherwise stated. *Defined by the US Centers for Disease and Control and Prevention.³¹ †Ten grade 3 or 4 transaminase elevations, two grade 3 or 4 bilirubin elevations, two grade 2 transaminases elevations, one grade 2 bilirubin elevation, and one grade 4 alkaline phosphatase elevation were observed.

Table 4: Adverse events

non-comparative ANRS 12180 Reflate TB trial, a higher proportion of patients had achieved virological suppression at week 48 in the raltegravir group while on tuberculosis treatment (76%) than the efavirenz group (67%).¹⁸ The INSPIRING non-comparative randomised trial evaluated double dose dolutegravir (50 mg twice daily) and efavirenz in adults with a median CD4 count of 208 cells per μL , the majority of whom had pulmonary tuberculosis. By week 48, 52 (75%) of 69 patients in the dolutegravir group and 36 (82%) of 44 patients in the efavirenz had achieved virological suppression.³⁶ Taken together, the results of this study and INSPIRING trials suggest that integrase inhibitor-based regimens, despite high anti-viral potency in patients without tuberculosis, result in a 5–7% lower rate of virological suppression at

week 48 than efavirenz-based regimens in patients with tuberculosis.^{24,25}

Our results contrast with raltegravir registration trials that enrolled participants with less advanced disease and without tuberculosis co-infection in high-income or middle-income countries. In the STARTMRK trial, 90.9% of patients on raltegravir-based regimens and 89.2% patients on efavirenz-based regimens achieved virological suppression.²⁴ Conversely, the lower rates of virological suppression observed in our study are consistent with results from the NAMSAL trial, which enrolled adults in Cameroon with a median HIV RNA concentration of 5.3 log₁₀ copies per mL.²⁶ Virological suppression was achieved in 74.5% of patients given dolutegravir 50 mg once daily and 69.0% of patients given efavirenz 400 once daily, which was lower than expected on the basis of previous studies of dolutegravir in ART-naïve patients, such as the ADVANCE study.²⁷ The main factor explaining these results was higher baseline viral loads.²⁶

In our study, high baseline viral loads seemed to have a similar effect: only 53% of patients with baseline HIV RNA concentrations of 500 000 copies per mL or higher achieved virological suppression at week 48. The effect of high baseline viral load seemed substantially higher in the raltegravir group: only 45% of patients with HIV RNA concentrations of 500 000 copies per mL or higher at baseline achieved virological suppression compared with 75% of patients with HIV RNA concentrations of less than 100 000 copies per mL at baseline. This difference in the proportion of patients with high baseline viral loads might also explain why lower suppression rates were observed than those observed in our previous phase 2 study, whereby the median baseline HIV RNA concentration was 4.9 log₁₀ copies per mL, with a lower proportion of patients with HIV RNA concentrations of more than 100 000 copies per mL.¹⁸

Despite similar rates of virological failure and similar proportions of patients with resistance to antiretrovirals in both study groups, a lower proportion of patients with virological failure in the raltegravir group had tenofovir resistance than did patients in the efavirenz group. The number of patients with dolutegravir-associated resistance mutations in patients with virological failure in the raltegravir group was also small, therefore preserving future use of dolutegravir-based second-line regimens.

The main limitations of our study are that we did not plan to assess pharmacokinetic parameters or to do a detailed quality of life substudy to investigate psychological or social factors that might affect treatment adherence. However, the interaction between antiretrovirals and rifampicin does not seem to explain our results. We identified no significant differences between treatment groups with regard to virological suppression at week 24, at a time when most patients remained on both antiretroviral and anti-tuberculosis medications. This is consistent with results from our previous study in

Brazilian individuals with HIV, which showed that drug–drug interactions with rifampicin had a smaller impact on the pharmacokinetic parameters of raltegravir than expected, and similar rates of virological suppression in patients given raltegravir 400 mg twice a day or efavirenz.^{18,19}

Adherence to treatment, a key contributor to virological suppression, was poorer among participants in the raltegravir group, who were dosed twice daily, than those in the efavirenz group who were dosed once daily, and might have contributed to the results observed in this study.²⁸ A meta-analysis suggested that in ART-naïve patients, taking treatment twice daily was associated with reduced adherence, but that the negative impact on virological suppression was associated with pill burden.²⁹ It is therefore unclear why adherence decreased in our study after week 24, when pill burden decreased following the discontinuation of anti-tuberculosis drugs, and whether recovery from tuberculosis and an increase in wellbeing led participants to be less adherent to their treatment.

Both antiretroviral strategies were safe. Few patients discontinued treatment due to adverse events. In our previous trial, two patients given raltegravir 800 mg twice a day with tuberculosis treatment had severe hepatotoxicity, which raised concerns about hepatic tolerance of high-dose raltegravir. In the present study, 4% of patients in both treatment groups had hepatic toxicity. Other severe adverse events, including severe cases of tuberculosis-associated immune reconstitution inflammatory syndrome, were also uncommon.

Integrase inhibitor-based ART has progressively become the preferred first-line antiretroviral regimen in international guidelines.¹⁴ The results of our study suggest, however, that integrase inhibitor-based regimens might not be as potent as expected in patients with tuberculosis due to adherence issues. The twice daily dosage seems to have disadvantaged the raltegravir-based regimen compared with the once daily efavirenz regimen. Preliminary programmatic data from Botswana showed 90% virological suppression at week 12 or 24 using a detection threshold of HIV RNA concentration of 400 copies per mL in patients taking dolutegravir 50 mg twice a day or once a day.³⁰ However, programmatic virological data at week 48 using a detection threshold of HIV RNA concentration of 50 copies per mL are scarce. Pending the availability of such data, and results from one other trial enrolling patients co-infected with tuberculosis (NCT03851588), the Reflate TB 2 study is the largest phase 3 trial providing information on integrase inhibitor-based therapy in this population. In the context of the dolutegravir rollout, virological response and adherence to the twice daily dosing for patients with tuberculosis needs to be monitored very closely by national HIV programmes. Emergence of high-level resistance to dolutegravir is rare, but has been previously described in the context of drug–drug interactions with rifampicin.³¹

In conclusion, despite promising virological and pharmacokinetic data from our previous phase 2 study, this phase 3 trial did not demonstrate non-inferiority of raltegravir 400 mg twice daily when compared with efavirenz in patients with HIV and tuberculosis co-infection. Our data indicate that efavirenz 600 mg once daily should remain an option for ART in patients with HIV and tuberculosis co-infection. In these patients with advanced disease, adherence to ART and baseline viral load seem to have an effect on virological response, which requires further investigation. Raltegravir was well tolerated and thus could be considered as an option, in selected patients only.

Contributors

NDC, OM, DL, XA, BG, and J-MM conceived and designed the study. BG and NDC led the study at international level. NDC, OM, and CC accessed and verified the data. VV and BG led the study in Brazil, EM and SE led the study in Côte d'Ivoire, NDC and J-MM led the study in France, NB and CK led the study in Mozambique, and GDC and DL led the study in Vietnam. OM coordinated study implementation at international level, RE coordinated study implementation in Brazil, JBN coordinated study implementation in Côte d'Ivoire, IT coordinated study implementation in Mozambique, and AD coordinated study implementation in Vietnam. CD coordinated the virological analyses. NDC, OM, BG, J-MM, CC, CD, and DL contributed to the interpretation of the results. EM, SE, NB, CK, GDC, SW, RE, VV, BG, NDC, J-MM implemented the study and enrolled participants. CC did the statistical analysis. CC and OM prepared the report. NDC wrote the first draft and all authors reviewed and approved the final version of the manuscript. NDC, OM, CC, DL, XA, BG, VV, CD, and J-MM full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

NDC reports grants from Gilead (Voice program 2015). CD has served on advisory boards for ViiV Healthcare, Gilead Sciences, Bristol-Myers Squibb, and Merck; and has received grants from Gilead and Merck, Sharp and Dohme. J-MM has served as a consultant, served on advisory boards, received speaker fees, and has been an investigator for clinical trials for Janssen, ViiV Healthcare, Gilead Sciences, Bristol-Myers Squibb, Abbott Laboratories, Boehringer Ingelheim, and Merck, Sharp and Dohme; and has received grants from Merck. All other authors declare no competing interests.

Data sharing

Study data will not be publicly available. Data could be made available by the sponsor (ANRS) to any researcher interested. Deidentified participant data and a data dictionary can be made available and shared under a data transfer agreement. Requests for access to the Reflate TB 2 study data should be sent to nathalie.de-castro@aphp.fr. The study protocol, statistical analysis plan, and informed consent forms are available in the appendix.

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8 Factors associated to virologic success and antiretroviral therapy adherence in people with HIV and tuberculosis

8.1 Research question and background

In the Reflate TB 2 study we failed to demonstrate the non-inferiority of raltegravir compared to efavirenz. We also observed that virologic efficacy was lower than expected in both arms and that virologic suppression decreased with increasing baseline HIV-1 RNA.

Many studies reported factors associated with virologic failure, the most frequently identified being the levels of HIV-1 RNA at ART initiation, the presence of baseline resistance, and adherence to ART. Different indirect measures of adherence have also been evaluated but there is no consensus on the gold standard. Pill counts and adherence questionnaires are the most frequently evaluated adherence monitoring methods because they are simpler to use. A recent trial conducted in Africa has shown that lower adherence as well as high baseline viral loads may be more an issue than what was expected, even with dolutegravir containing regimens. Similarly, the Reflate TB2 trial failed to show non-inferiority of raltegravir versus efavirenz in PLWH with tuberculosis, with less than 70% of the patients achieving HIV-1 RNA < 50 copies/mL at week 48 on both regimens. The PK interaction between raltegravir and rifampicin was unlikely to explain this finding, as suggested by PK data from the phase II Reflate TB trial. Moreover, the week 24 results showed no difference between the raltegravir and efavirenz arms while patients received both ART and rifampicin. Adherence, measured using pill count adherence ratio, decreased in both trial arms after week 24 and was lower overall in the raltegravir arm compared to the efavirenz arm. Following these observations, our objective was to better understand which factors were associated to virologic success and also analyse determinants of adherence in the Reflate TB 2 trial.

8.2 Determinants of antiretroviral treatment success and adherence in People With Human Immunodeficiency Virus treated for tuberculosis. *OFID* 2022;9;ofac628.

This study focused on 444 participants from the ANRS 1300 Reflate TB2 trial. Part of the results were presented at the 23rd International AIDS conference virtual 6-10 July 2020. and at the 18th European Aids Conference, London October 27-30, 2021. This paper has been accepted in *Open Forum Infect Dis* for publication and has been submitted with the changes requested by the reviewers. Final approval is pending. The supplementary material provided with the paper is presented in appendix 8.

Determinants of Antiretroviral Treatment Success and Adherence in People With Human Immunodeficiency Virus Treated for Tuberculosis

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Background. In people with human immunodeficiency virus [HIV] presenting with advanced disease, rates of virologic success may be lower than expected. The Reflate TB2 trial did not show non-inferiority of raltegravir versus efavirenz in people with HIV (PWH) treated for tuberculosis. We aimed to identify factors associated with virologic success and higher adherence in the trial.

Methods. In this analysis, we included participants enrolled in the Reflate TB2 trial with adherence data available. The primary outcome was virologic success (HIV-1 ribonucleic acid [RNA] <50 copies/mL) at week 48, and the secondary outcome was adherence as assessed by the pill count adherence ratio. We used logistic regression to study determinants of virologic success and optimal adherence in 2 separate analyses.

Results. Four hundred forty-four participants were included in the present analysis. Over the 48-week follow-up period, 290 of 444 (65%) participants had a pill count adherence ratio $\geq 95\%$. At week 48, 288 of 444 (65%) participants were in virologic success. In the multivariate analysis, female sex (adjusted odds ratio [aOR], 1.77; 95% confidence interval [CI], 1.16–2.72; $P = .0084$), lower baseline HIV-1 RNA levels (<100 000; aOR, 2.29; 95% CI, 1.33–3.96; $P = .0087$), and pill count adherence ratio $\geq 95\%$ (aOR, 2.38; 95% CI, 1.56–3.62; $P < .0001$) were independently associated with virologic success. Antiretroviral pill burden was the only factor associated with pill count adherence ratio $\geq 95\%$ (OR, 0.81; 95% CI, .71–.92; $P = .0018$).

Conclusions. In PWH with tuberculosis receiving raltegravir or efavirenz-based regimens, female sex, optimal adherence, and baseline HIV-1 RNA <100 000 copies/mL were associated with virologic success, and the number of antiretroviral tablets taken daily was a strong predictor of adherence.

Keywords. adherence; HIV viral load; raltegravir; tuberculosis.

Tuberculosis remains a major cause of morbidity and the leading cause of death in people with human immunodeficiency

virus (PWH). In 2020, 214 000 of the 680 000 deaths reported in PWH were due to tuberculosis [1]. Better access to tuberculosis diagnosis, appropriate tuberculosis treatment, and early initiation of antiretroviral therapy (ART) are key to reduce tuberculosis-related mortality [2–4]. Antiretroviral therapy options are limited in PWH with tuberculosis due to drug-drug interactions with rifampicin, which lead to reduced plasma drug levels for most antiretrovirals.

Until recently, efavirenz, a nonnucleoside reverse-transcriptase inhibitor, was the preferred first-line ART recommended by the World Health Organization (WHO) in (1) PWH overall and in (2) those with tuberculosis due to less potential drug-drug interactions with rifampicin requiring no dose adaptation [5]. In 2017, the WHO recommended the second-generation integrase inhibitor dolutegravir at the standard dose of 50 mg in association with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) for all adults as first-line

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ART [5]. Due to drug-drug interactions with rifampicin, standard dose dolutegravir cannot be used in PWH with tuberculosis, and the WHO recommended double-dose dolutegravir (50 mg twice daily) as the first-line option to treat patients co-infected with tuberculosis and human immunodeficiency virus (HIV), based on the moderate certainty of evidence from a noncomparative randomized study [5–7].

The ANRS 12300 Reflate TB2 trial was a large, phase 3 trial that evaluated the use of another integrase inhibitor, raltegravir, in PWH with tuberculosis. This trial did not show the noninferiority at week 48 of twice-daily raltegravir 400 mg compared with once-daily efavirenz 600 mg, whereas a similar proportion of patients achieved HIV-1 RNA-1 <50 copies/mL at week 24 in the 2 arms [8]. Rates of virologic success at week 48 were lower in patients with baseline viral load $\geq 100\,000$ copies/mL and when adherence to ART was suboptimal, which may have contributed to the results observed in trial, with significantly lower adherence in the raltegravir arm compared with the efavirenz arm throughout the study [8].

Adherence to ART is a main driver of virologic efficacy and suboptimal adherence is associated to virologic failure [9–12]. Various indirect measures of adherence have been used, including patients' self-reports, pill count adherence or medication possession ratio, pharmacy refill, physician evaluation, or electronic measures [13–17]. There is no gold standard measure of adherence; thus, addition of different measures may be more robust than 1 single evaluation (for example, self-reported adherence or pill-count) to correlate with virologic failure [18–22]. The threshold to define optimal adherence has been largely debated, but it is accepted that an adherence equal to or above 95% can be considered an optimal adherence level enabling to achieve virologic control [22, 23]. A further understanding of the determinants of adherence and measuring their influence on virologic efficacy is challenging because socio-demographic and economic factors are also involved [9–12].

Adherence issues at ART initiation might have been underestimated recently with better tolerated, convenient, and more robust once-daily fixed-dose ART combinations accessible. Those regimens may allow for more flexibility and nonoptimal adherence, notably in patients with less advanced disease starting ART at low HIV-1 ribonucleic acid (RNA) levels. Reflate TB2 and other recent studies conducted in Africa suggest that in patients with very high HIV-1 RNA at ART initiation, suboptimal adherence may be more of an issue and that lower adherence is a good predictor of virologic failure, even in patients receiving integrase inhibitors [8, 24, 25].

We hypothesized that high baseline HIV-1 RNA and suboptimal adherence in the context of twice-daily raltegravir might explain the negative results of the Reflate TB2 trial. We sought to further identify factors associated with virologic success and optimal adherence to ART.

METHODS

Study Design and Population

We conducted a secondary analysis of the ANRS 12.300 Reflate TB2. The trial design and study results have been reported previously [8]. Between September 2015 and January 2018, ART-naive HIV-1-infected adults age ≥ 18 years with tuberculosis initiated on antituberculosis treatment within the prior 8 weeks were randomized to initiate ART with either raltegravir 400 mg 1 pill twice daily or efavirenz 600 mg once daily, both in association with TDF 300 mg once daily and 3TC 300 mg once daily. Tenofovir disoproxil fumarate/3TC/efavirenz or TDF/3TC were available as single pill fixed-dose combinations depending on countries and stock. Stock outs in some countries of fixed-dose combination for once-daily TDF/3TC led to temporarily use TDF 1 tablet per day once daily and 3TC 150 mg 1 tablet twice daily in association with raltegravir 1 tablet twice daily (total of 5 tablets daily).

In the present study, we included all patients enrolled in the Reflate TB2 trial in Brazil, Côte d'Ivoire, Mozambique, and Vietnam, excluding those with HIV-1 RNA <50 copies/mL at baseline ($n = 3$) and those with missing data on ART accountability ($n = 9$). We excluded patients enrolled in France ($n = 4$) because we wished to restrict the analysis to low- and middle-income countries and because the low number of French participants would not allow for comparisons.

Patient Consent Statement

The Reflate TB2 study protocol was approved by relevant National and Local Ethics Committees in all participating countries and registered with ClinicalTrials.gov (NCT02273765). All participants provided signed informed consent before enrollment in the main trial.

Study Procedures

We performed clinical and laboratory assessments for all patients at all study visits. We monitored adherence to ART in patients using pill count; patients were thus requested to return their remaining pills to the pharmacy at all study visits from week 2 to week 48 (weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48). In addition, we evaluated self-reported adherence to ART with 4 days and 1 month recall periods at all study visits after week 2 (Supplementary Appendix) [14]. Adherence to tuberculosis treatment was also monitored using the Taxo INH Test Strips (Becton Dickinson, Franklin Lakes, NJ) to detect isoniazid metabolites in urines at weeks 0 and at study visits closest to months 2 and 5 of tuberculosis treatment [26]. Isoniazid (INH) metabolites are detected in urine up to 36 hours postdrug intake. The production of Taxo INH Test Strips was interrupted during the trial, and isoniazid urine strips were no longer used after March 3, 2017. Treatments were reported in the case report form for all participants, at

each study visit, including the number of pills prescribed for antiretrovirals, antituberculosis drugs, and oral concomitant treatments, which allowed for computing treatments durations and pill burden.

Outcomes and Definitions

The primary outcome of the present study was virologic success at week 48, defined as plasma HIV-1 RNA <50 copies/mL on allocated study drugs per the US Food and Drug Administration Snapshot algorithm [27]. Our secondary outcome was adherence to ART as assessed by pill count adherence ratio (Supplementary Appendix). We defined high or optimal adherence as a pill count adherence ratio $\geq 95\%$ and low or sub-optimal adherence as a pill count adherence ratio <95% [22]. Self-reported nonoptimal adherence was defined as missing at least 1 dose of treatment during the recall time (4 days and/or 1 month self-reported nonadherence). We also calculated treatment related pill burden for ART, tuberculosis treatment, and other concomitant treatments (full definitions in Supplementary Appendix).

Statistical Analysis

We described baseline characteristics in each group for the 2 main analysis on virologic success, and optimal adherence using frequency and proportions for qualitative variables, and median and interquartile range (IQR) for quantitative variables. We compared characteristics across groups using Wilcoxon tests (comparison of medians) for quantitative variables, and we used the χ^2 or the Fisher's exact test for qualitative variables as appropriate.

We used logistic regression to study determinants of virologic success and optimal adherence in 2 separate analyses (Supplementary Appendix). We selected variables based on previous evidence from the literature and clinical relevance. We derived a final model that resulted from a stepwise descending selection retaining all variables with a level of significance $P = .05$. We analyzed data with the SAS software (version 9.4M3).

RESULTS

Of 460 participants enrolled in the Reflate TB2 trial, we included 444 in the present analysis (Supplementary Figure 1). The study participants had advanced HIV disease with median CD4⁺ T-cell count of 102 (IQR, 38–242) cells per cubic millimeter, and median plasma HIV-1 RNA was 5.5 (IQR, 5.0–5.8) log₁₀ copies/mL, with 330 of 444 (74%) participants with HIV-1 RNA above 100 000 copies/mL (Table 1). Participants were started on ART at a median of 20 (IQR, 15–27) days after tuberculosis treatment initiation.

Overall, 222 of 444 (50%) patients received a raltegravir-based regimen for a median of 48 months and 222 of 444 (50%) received an efavirenz-based regimen for a median of

48 months ($P = .3103$). The median ART pill burden was 1.0 (IQR, 1.0–3.0) tablets per day, 1 (IQR, 1–1) tablet per day for patients on efavirenz, and 3.0 (IQR, 3.0–5.0) tablets per day for patients on raltegravir. Patients received tuberculosis treatment for a median duration of 26 (IQR, 26–27) weeks from randomization. During the trial, the median tuberculosis treatment pill burden was 4.0 (IQR, 3.0–4.2) tablets per day and concomitant treatment pill burden was 0.5 tablets per day (IQR, 0.1–1.5).

Over the 48-week follow-up period, the median ART pill count adherence ratio was 98.6% (IQR, 91.6%–101.6%); 290 (65%) of the participants had optimal adherence with a pill count adherence ratio $\geq 95\%$. The proportion of optimal adherent participants decreased after week 24, from 72% during the first 24 weeks of the study to 66% during the last 24 weeks of the study.

At week 48, 288 (65%) participants had HIV-1 RNA <50 copies/mL on allocated therapy. Of the 156 (35%) participants who did not achieve virologic success, 20 (5%) died, 75 (17%) had HIV-1 RNA ≥ 50 copies/mL at week 48, and 39 (9%) had discontinued raltegravir or efavirenz treatment before week 48, including 22 (5%) who had been switched to second-line ART for lack of efficacy (9 on efavirenz and 13 on raltegravir-based ART). Considering other thresholds for virologic success at week 48, 319 of 444 (72%) and 326 of 444 (73%) participants had HIV-1 RNA of <200 copies/mL and <1000 copies/mL, respectively (Supplementary Table 1).

Patients with virologic success differed from those who did not achieve virologic success on 3 major characteristics: (1) the proportion of female participants was higher in the group achieving virologic success (44% vs 31%; $P = .0091$) (Table 1), (2) the median baseline HIV-1 RNA before ART was lower in those who achieved virologic success (5.4 log₁₀ copies/mL vs 5.6 log₁₀ copies/mL; $P = .0009$), and (3) the proportion of participants with optimal adherence and a pill count adherence $\geq 95\%$ over the 48 weeks of the study was higher in those in virologic success (72% vs 53%; $P < .0001$) (Table 1). Hemoglobin levels and CD4 cell counts differed statistically between the 2 groups, but the differences were not clinically relevant. In the multivariate analysis, optimal adherence measured by pill count adherence ratio $\geq 95\%$ (adjusted odds ratio [aOR], 2.38; 95% confidence interval [CI], 1.56–3.62; $P = .0084$), lower baseline HIV-1 RNA levels (HIV-1 RNA < 100 000; aOR, 2.29; 95% CI, 1.33–3.96; $P = .009$), and female sex (aOR, 1.77; 95% CI, 1.16–2.72; $P < .0001$) were independently associated with virologic success (Table 2).

In the analysis on factors associated with optimal ART adherence, a strong predictor of virologic success, we found no difference in terms of demographic characteristic and tobacco, alcohol or other substances use, baseline body mass index, and CD4 counts between participants with optimal adherence compared to those with non-optimal adherence (Table 3). The

Table 1. Patients Characteristics by HIV-1 RNA at Week 48^a

	N*	Virologic Success (N=288)	N*	Not in Virologic Success (N=156)	N*	Total (N=444)	P Value
Antiretroviral Treatment							
Efavirenz	...	150 (52%)	...	49 (31%)	...	199 (45%)	
Raltegravir	...	138 (48%)	...	65 (42%)	...	203 (46%)	
Country							
Ivory Coast	...	98 (34%)	...	66 (42%)	...	164 (37%)	P= .2646 (K)
Brazil	...	32 (11%)	...	11 (7%)	...	43 (10%)	
Vietnam	...	74 (26%)	...	36 (23%)	...	110 (25%)	...
Mozambique	...	84 (29%)	...	43 (28%)	...	127 (29%)	
Age (years)	...	35 (29–43)	...	35 (29–44)	...	35 (29–43)	P= .9456 (W)
Female sex	...	127 (44%)	...	49 (31%)	...	176 (40%)	P= .0091 (K)
Body mass index (kg/m ²)	287	19.1 (17.6–21.1)	...	18.9 (17.3–20.6)	443	19.1 (17.5–21.0)	P= .2055 (W)
Hemoglobin (g/dL)	...	9.8 (8.6–11.4)	...	9.8 (8.4–11.1)	...	9.8 (8.5–11.3)	P= .4260 (W)
CD4 ⁺ T-cell count (cells per mm ³)	287	117 (47–245)	...	80 (26–212)	443	102 (38–242)	P= .0259 (W)
≤200 cells per mm ³	287	186 (65%)	...	116 (74%)	443	302 (68%)	
≤50 cells per mm ³	287	89 (31%)	...	57 (37%)	443	146 (33%)	
Plasma HIV-1 viral load (log ₁₀ copies per mL)	287	5.4 (4.9–5.8)	154	5.6 (5.2–5.9)	441	5.5 (5.0–5.8)	P= .0009 (W)
<100 000 copies per mL	287	82 (29%)	154	29 (19%)	441	111 (25%)	
[100 000; 500 000]	287	122 (43%)	154	58 (38%)	441	180 (41%)	
≥500 000 copies per mL	287	83 (29%)	154	67 (44%)	441	150 (34%)	
On cotrimoxazole prophylaxis	...	258 (90%)	...	134 (86%)	...	392 (88%)	P= .2489 (K)
Current anatomical site of tuberculosis disease							
Pulmonary only	...	196 (68%)	...	113 (72%)	...	309 (70%)	P= .5733 (K)
Extrapulmonary only	...	54 (19%)	...	27 (17%)	...	81 (18%)	
Pulmonary and extrapulmonary	...	38 (13%)	...	16 (10%)	...	54 (12%)	
Bacteriologically confirmed tuberculosis	286	197 (69%)	154	106 (69%)	440	303 (69%)	P= .9914 (K)
Time on tuberculosis treatment at enrollment (days)	...	20 (15–27)	...	20 (15–27)	...	20 (15–27)	P= .7075 (W)
Alanine aminotransferase level (U/L)	287	25 (16–41)	154	22 (14–33)	441	24 (15–38)	P= .0409 (W)
Creatinine clearance (mL/min/1.73 m ²)	...	99.1 (81.8–122.8)	...	100.7 (78.4–125.6)	...	99.6 (80.7–123.1)	P= .9410 (W)
Pill count adherence ratio week 0–week 48							
≥95%	...	208 (72%)	...	82 (53%)	...	290 (65%)	P< .0001 (K)
[80%–95%]	...	62 (22%)	...	45 (29%)	...	107 (24%)	
<80%	...	18 (6%)	...	29 (19%)	...	47 (11%)	
Pill count adherence ratio week 0–week 24							
≥95%	...	228 (79%)	155	93 (60%)	...	321 (72%)	P< .0001 (K)
[80%–95%]	...	49 (17%)	155	33 (21%)	...	82 (18%)	
<80%	...	11 (4%)	155	30 (19%)	...	41 (9%)	
Pill count adherence ratio week 24–week 48							
≥95%	...	207 (72%)	119	60 (50%)	407	267 (66%)	P< .0001 (K)
[80%–95%]	...	51 (18%)	119	22 (18%)	407	73 (18%)	
<80%	...	30 (10%)	119	37 (31%)	407	67 (16%)	

Abbreviations: F, Fisher's exact test; HIV, human immunodeficiency virus; K, χ^2 test; RNA, ribonucleic acid; W, Wilcoxon test.

^aData are n (%) or median (interquartile range).

median ART pill burden differed significantly between participants with optimal adherence (1.0 [IQR, 1.0–3.0] tablet per day) and participants with lower adherence (3.0 [IQR, 1.0–3.0] tablets per day; $P = .0005$), but there was no difference in median tuberculosis treatment pill burden and concomitant treatment pill burden between the 2 groups (Table 3). In the multivariate analysis, only higher ART pill burden was associated with lower adherence (OR, 0.81; 95% CI, .71–.92; $P = .0018$) (Table 4).

Patients with pill count adherence ratio $\geq 95\%$ also had better self-reported adherence (Table 5). The proportion of participants with 4-day, self-reported nonadherence throughout the

48 weeks of the study was lower in participants with pill count adherence ratio $\geq 95\%$: 51 of 290 (18%) compared to 51 of 154 (33%) for participants with pill count adherence ratio $< 95\%$ ($P = .0002$) (Table 5). One-month, self-reported nonadherence was also higher in participants with pill count adherence ratio $< 95\%$: 55 of 154 (36%) compared to 62 of 290 (21%) for participants with optimal adherence ($P = .0011$) (Table 5). Reported adherence to tuberculosis treatment was also higher in patient with optimal adherence to ART; 4-day, self-reported nonadherence to tuberculosis treatment was 4% and 10% in participants with optimal adherence and those with suboptimal adherence, respectively ($P = .0187$). There was no difference

Table 2. Factors Associated to Virologic Success

...	Total N	Virologic Success N (%/N) or Median (q1, q3)	Univariate Analysis				Multivariate Analysis			
			OR	Lower 95% CI	Upper 95% CI	Pr > χ^2	OR	Lower 95% CI	Upper 95% CI	Pr > χ^2
Treatment
Efavirenz	222	150 (68%)	1	0.2332
Raltegravir	222	138 (62%)	0.79	0.53	1.17
Country
Brazil	43	32 (74%)	1	0.2694
Ivory Coast	164	98 (60%)	0.51	0.24	1.08
Mozambique	127	84 (66%)	0.67	0.31	1.46
Vietnam	110	74 (67%)	0.71	0.32	1.56
Sex
Male	268	161 (60%)	1	0.0094
Female	176	127 (72%)	1.72	1.14	2.60	...	1.77	1.16	2.72	0.0084
Age (Years)
Age >35	223	149 (67%)	1	0.3871
Age ≤35	221	139 (63%)	0.84	0.57	1.24
BMI (kg/m ²)
BMI > 18.5	259	172 (66%)	1	0.3961
BMI ≤ 18.5	184	115 (63%)	0.84	0.57	1.25
CD4 counts (/mm ³)
CD4 <50	142	87 (61%)	1	0.1208
CD4: [50 to 200]	160	99 (62%)	0.97	0.61	1.55
CD4 ≥200	141	101 (72%)	0.63	0.38	1.03
Viral Load at Baseline
HIV-1 VL ≥500 000	150	83 (55%)	1	0.0054
<100 000	111	82 (74%)	2.28	1.34	3.88	...	2.29	1.33	3.96	0.0087
100 000 to 500 000	180	122 (68%)	1.70	1.08	2.66	...	1.62	1.02	2.57	0.0087
Pill count ratio
Pill count ratio <95%	154	80 (52%)	1
Pill count ratio ≥95%	290	208 (72%)	2.35	1.56	3.52	<.00001	2.38	1.56	3.62	0

Abbreviations: BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; VL, viral load.

between participants with optimal and suboptimal adherence regarding baseline detection of isoniazid metabolites in urines (Table 5).

Self-reported adherence according to ART is shown in Supplementary Figure S2.

DISCUSSION

In this secondary analysis of the Reflate TB2 trial, we showed that optimal adherence to ART as well as lower baseline HIV-1 RNA and female sex were associated with virologic success. We also showed that the main determinant of optimal adherence was ART pill burden, hence hampering success in the raltegravir-based regimen that requires twice-daily intake of 3 tablets.

Virologic success was achieved in 65% of the patients, which was lower than expected 1 year after ART initiation in HIV-1-infected naive patients receiving efavirenz or raltegravir, and it contrasts with pivotal studies in which more than 80% of the participants achieved virologic suppression on both regimens [28, 29]. We found that 73% of the patients had HIV-1 RNA below 1000 copies/mL at week 48, much lower

than the UNAIDS/WHO 90-90-90 third target to have globally 90% of PWH with viral load below 1000 copies per mL 1 year after initiation of ART. One explanatory factor was that a high proportion of patients had baseline viral load above 100 000 copies/mL including 34% with baseline HIV-1 RNA above 500 000 copies/mL, and indeed in the multivariate model, HIV-1 RNA of less than 100 000 copies/mL was associated to virologic success. The impact of high baseline HIV-1 viral load on virologic success rates was also found in previous studies [25, 30].

It is interesting to note that our analysis showed that female sex was associated with better virologic outcomes but not with higher adherence. It was also reported previously that men were more likely to experience virologic failure than women, without clear explanation. Tuberculosis coinfection has been reported to be a factor associated with virologic failure in some studies [31–34]. The reasons for these associations remain unclear.

We found that only 65% of the participants had optimal adherence to ART, which was one other factor associated to virologic success. This finding is consistent with previous reports

Table 3. Patient Characteristics by Pill Count Adherence Ratio

	N*	Pill Count Ratio ≥95% (N=290)	N*	Pill Count Ratio <95% (N=154)	
Antiretroviral Treatment	
Efavirenz	...	162 (56%)	...	60 (39%)	<i>P</i> = .0007 (K)
Raltegravir	...	128 (44%)	...	94 (61%)	
Country	
Ivory Coast	...	99 (34%)	...	65 (42%)	<i>P</i> = .2372 (K)
Brazil	...	30 (10%)	...	13 (8%)	
Vietnam	...	79 (27%)	...	31 (20%)	
Mozambique	...	82 (28%)	...	45 (29%)	
Sex	
Male	...	176 (61%)	...	92 (60%)	<i>P</i> = .8457 (K)
Female	...	114 (39%)	...	62 (40%)	
Age (years)	...	35 (29–43)	...	36 (30–43)	<i>P</i> = .3087 (W)
BMI (kg/m ²)	289	19.2 (17.4–20.8)	...	18.8 (17.7–21.0)	<i>P</i> = .8783 (W)
Tobacco smoking	
Never	289	208 (72%)	153	114 (75%)	<i>P</i> = .3835 (F)
Yes, but stopped	289	70 (24%)	153	37 (24%)	
Yes, ongoing	289	11 (4%)	153	2 (1%)	
Alcohol Consumption	
Never	...	132 (46%)	153	56 (37%)	<i>P</i> = .0710 (K)
Yes, past or ongoing	...	158 (55%)	153	97 (63%)	
Drug use	
Never	...	265 (91%)	153	134 (88%)	<i>P</i> = .2038 (K)
Yes, past or ongoing	...	25 (9%)	153	19 (12%)	
CD4 (mm ³) at PI	289	111 (39–248)	...	89 (35–215)	<i>P</i> = .1505 (W)
ART pill burden ^a	...	1.0 (1.0–3.0)	...	3.0 (1.0–3.0)	<i>P</i> = .0005 (W)
...	...	1.0–5.0	...	1.0–5.0	
TB pill burden ^b	289	4.0 (3.0–4.4)	...	3.9 (3.0–4.0)	<i>P</i> = .1534 (W)
Min-max	...	2.0–9.9	...	2.0–8.7	
CT pill burden ^c	...	0.5 (0.1–1.5)	...	0.5 (0.1–1.7)	<i>P</i> = .5713 (W)
min-max	...	0.0–14.5	...	0.0–8.4	

Abbreviations: ART, antiretroviral treatment; BMI, body mass index; CT, concomitant treatment; F, Fisher's exact test; K, χ^2 test; max, maximum; min, minimum; PI, protease inhibitor; TB, tuberculosis; W, Wilcoxon test.

NOTE: Data are *n* (%) or median (interquartile range).

^aNumber of pills per day during allocated therapy treatment.

^bNumber of pills per day during TB treatment.

^cNumber of pills per day during the study.

showing that lower ART adherence contributes to virologic failure [18, 31, 35, 36]. In our study, lower ART pill burden was the only factor associated to optimal adherence, hence disadvantaging the raltegravir-based regimen. Importantly, 28% of the patients on raltegravir received 5 pills per day because of stock outs of the coformulated 3TC/TDF pill, possibly further hampering adherence to the combination. We could not separately evaluate the effect of ART pill burden and daily dosing of ART regimen because the number of pills taken daily was de facto different according to the ART regimen prescribed. However, other studies showed that twice-daily dosing ART rather than pill burden was associated to lower adherence [37–41]. Lower patient satisfaction with the twice-daily regimen seems to explain this finding [41]. Although we did not evaluate participants' satisfaction about ART, our data also suggest the same impact of the twice-daily dosing of raltegravir regimen.

Optimal adherence defined as pill count adherence ratio $\geq 95\%$ was concordant with other markers of adherence, especially with reporting at least 1 lapse in ART or tuberculosis treatment intake over the past 4 days or month. Also of note, we found that adherence decreased after week 24 when most patients were off tuberculosis treatment, which is difficult to interpret because we did not evaluate patients' motivations. For PWH presenting with advanced disease, the WHO now strongly recommends intensified adherence interventions during the first months of ART, including home- or community-based follow-up and early tracing in case of missed visits, in addition to initial counseling at ART initiation [24, 42–45]. Our results, along with previous recent studies, show that using pill count adherence ratio and self-adherence questionnaires at each visit could help to target such interventions by identifying patients who may benefit the most from adherence support [16, 21, 42].

Table 4. Factors Associated to Pill Count Ratio $\geq 95\%$

...	Total N	Pill Count $\geq 95\%$ N (%N) or Median (q1, q3)	Univariate Analysis				Multivariate Analysis			
			OR	Lower 95% CI	Upper 95% CI	Pr > χ^2	OR	Lower 95% CI	Upper 95% CI	Pr > χ^2
ART pill burden ^a	290	1.0 (1.0–3.0)	0.81	0.71	0.92	0.0018	0.81	0.71	0.92	0.0018
Country
Brazil	43	30 (70%)	1
Ivory Coast	164	99 (60%)	0.69	0.34	1.43	0.2806
Mozambique	127	82 (65%)	0.82	0.39	1.73	0.2806
Vietnam	110	79 (72%)	1.14	0.53	2.48	0.2806
Sex
Male	268	176 (66%)	1
Female	176	114 (65%)	0.98	0.66	1.47	0.9310
Age (years)
Age >35	223	141 (63%)	1
Age ≤ 35	221	149 (67%)	1.18	0.80	1.75	0.4064
BMI (kg/m ²)
BMI >18.5	259	170 (66%)	1
BMI ≤ 18.5	184	119 (65%)	0.95	0.64	1.41	0.7906
Alcohol Consumption
Alcohol: yes (stopped or ongoing)	188	158 (62%)	1
Alcohol: never	255	132 (70%)	1.44	0.96	2.15	0.0778

Abbreviations: ART, antiretroviral treatment; BMI, body mass index; CI, confidence interval; OR, odds ratio.

^aN, median (q1, q3) antiretroviral pill burden for pill count <95%: 154, 3.0 (1.0–3.0).

Our study has limitations. First, we did not analyze baseline HIV-1 resistance and its contribution to virologic failure, but in patients who failed we had found in the Reflate TB2 trial that baseline resistance to non-nucleoside reverse-transcriptase inhibitors and integrase inhibitors was 10% and 3%, respectively [8]. Second, adherence measurements in the study may not have been very accurate: (1) pharmacy refills and patients self-reported adherence do not provide an exact measure of the number of pills taken by the patients, (2) we measured adherence over large periods of 6 or 12 months, and (3) we may not identify short treatment interruptions and thus overestimate adherence in some patients. Finally, we did not explore psychosocial determinants of adherence and how they might have contributed to our results.

CONCLUSIONS

Antiretroviral therapy remains challenging in PWH co-infected with tuberculosis, with a risk of reduced exposure to antiretroviral drugs due to drug-drug interactions with rifampicin or tolerance issues. This prompted the search of alternative regimens to efavirenz over the past decade and resulted in the use of better tolerated integrase inhibitor-based regimens. We found that during the first year after tuberculosis diagnosis, patients with optimal adherence and those with lower baseline HIV-1 viral load had higher odds of virologic success. The number of ART tablets taken daily was a strong predictor of

adherence and was due to the twice-daily dosing of the raltegravir-based ART regimen. We provide evidence that adherence monitoring using pill count adherence ratio and self-adherence questionnaires may help clinicians to identify patients at risk for virological failure; this group of patients needs targeted adherence counseling within the first months of ART. Despite the fact that dolutegravir is a more robust drug than raltegravir, with higher genetic barrier for resistance, our results raise concerns about adherence to the twice-daily, dolutegravir-based ART now recommended by the WHO for patients treated for tuberculosis. Future studies analyzing data from the national HIV and tuberculosis programs will be important to better describe outcomes in PWH coinfected with tuberculosis and treated with the twice-daily dosage of dolutegravir.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Table 5. Description of Measures of Nonadherence^a

...	N*	Pill Count Ratio ≥95% (N=290)	N*	Pill Count Ratio <95% (N=154)	N*	Total (N=444)	P
Self-reported nonadherence to ART between week 0 and week 48
In the last 4 d or 1 mo	...	68 (23%)	...	58 (38%)	...	126 (28%)	P=.0016 (K)
In the last 4 d	...	51 (18%)	...	51 (33%)	...	102 (23%)	P=.0002 (K)
In the last month	...	62 (21%)	...	55 (36%)	...	117 (26%)	P=.0011 (K)
Self-reported nonadherence to ART between week 0 and week 24
In the last 4 d or 1 mo	...	48 (17%)	...	42 (27%)	...	90 (20%)	P=.0075 (K)
In the last 4 d	...	35 (12%)	...	33 (21%)	...	68 (15%)	P=.0091 (K)
In the last month	...	44 (15%)	...	40 (26%)	...	84 (19%)	P=.0057 (K)
Self-reported nonadherence to ART between week 24 and week 48
In the last 4 d or 1 mo	278	27 (10%)	133	34 (26%)	411	61 (15%)	P<.0001 (K)
In the last 4 d	278	17 (6%)	133	31 (23%)	411	48 (12%)	P<.0001 (K)
In the last month	278	23 (8%)	133	30 (23%)	411	53 (13%)	P<.0001 (K)
Self-reported nonadherence to TB treatment between week 0 and end of TB treatment
In the last 4 d or 1 mo	...	16 (6%)	...	19 (12%)	...	35 (8%)	P=.0111 (K)
In the last 4 d	...	12 (4%)	...	15 (10%)	...	27 (6%)	P=.0187 (K)
In the last month	...	14 (5%)	...	18 (12%)	...	32 (7%)	P=.0078 (K)
Inclusion: urine INH result, positive (blue)	160	151 (94%)	74	69 (93%)	234	220 (94%)	P=.7702 (F)

Abbreviations: ART, antiretroviral therapy; d, days; INH, isoniazid; F, Fisher's exact test; K, χ^2 test; mo, months; TB, tuberculosis; W, Wilcoxon test.

^aData are n (%).

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9 Differences in virologic success according to country in people with HIV and tuberculosis treated with raltegravir or efavirenz

9.1 Research question and background: pooled data from the ANRS 12180 Reflate TB and the ANRS 12300 Reflate TB2 trials to assess the efficacy of the 2 strategies in different countries

The main drivers of virologic success in the ANRS 1300 Reflate TB 2 trial were baseline viral load levels and adherence to ART. However, results from Brazilian participants were different from those from other countries and this finding was consistent with what was found in the phase II ANRS 12180 Reflate TB study. Indeed, in Brazil, raltegravir performed better than efavirenz but the lower number of participants from Brazil compared to the other countries did not allow to conclude on the role of country. We pooled data from the phase II Reflate TB trial (conducted in 2009-2011) with data from the phase III Reflate TB2 trial (conducted in 2015-2018) to have a similar number of participants in each country. The pooled analyses allowed us to further explore differences between countries in terms of virologic success rates and also to study determinants of virologic success.

9.2 Differences in virologic response to antiretroviral therapy in people with HIV treated for tuberculosis in 4 high-TB burden countries – a pooled analysis of 2 randomised controlled trials. Submitted.

This paper reports analysis on 550 patients enrolled in the Reflate TB and the Reflate TB 2 trials and complements the work presented in the paper published in OFID. The paper was submitted to AIDS as a brief report. The appendix submitted with the paper is reported in appendix 7.

Differences in virologic response to antiretroviral therapy in people with HIV treated for tuberculosis in 4 high-TB burden countries – a pooled analysis of 2 randomized controlled trials

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Abstract

Objectives: We sought to compare virologic outcomes between PWH with tuberculosis on ART from the different countries who participated to the ANRS 12180 Reflate TB and ANRS 12300 Reflate TB2 trials.

Design: We pooled data from two randomized clinical trials evaluating raltegravir 400 mg twice daily and efavirenz 600 mg once daily in PWH treated for tuberculosis in Brazil, Côte d'Ivoire, Mozambique and Vietnam.

Methods: We assessed country differences in baseline characteristic and determinants of virologic success, defined as week-48 plasma HIV-1 RNA <50 copies/mL, using logistic regression.

Results: Of 550 participants (140 from Brazil, 170 from Côte d'Ivoire, 129 from Mozambique and 111 from Vietnam) with median baseline HIV-1 RNA of 5.4 log₁₀ copies/mL, 362 (65.8%) achieved virologic success at week 48. Virologic success rates were: 105/140 (75.0%) in Brazil, 99/170 (58.2%) in Côte d'Ivoire, 84/129 (65.1%) in Mozambique and 74/111 (66.7%) in Vietnam (p=0.0217). Baseline HIV-1 RNA, but not the country, was independently associated with virologic success: reference HIV-1 RNA ≥500,000 copies/mL, HIV RNA <100,000 copies/mL OR: 3.12 (95%CI 1.94; 5.01) and HIV-1 RNA 100,000-499,999 copies/mL OR: 1.80 (95% CI 1.19; 2.73). Overall, 177/277 (63.9%) patients treated with raltegravir and 185/273 (67.9%) patients treated with efavirenz had a plasma HIV-1 RNA <50 copies/mL at week 48.

Conclusions: Virologic response to antiretroviral therapy in PWH with TB varied across countries but was mainly driven by levels of pre-treatment HIV-1 RNA.

Key words: Virologic success, HIV viral load, tuberculosis

INTRODUCTION

Integrase inhibitors (INSTIs) based-regimens are now the standard antiretroviral therapy (ART) recommended in all guidelines to treat HIV infection in all people with HIV (PWH). Both raltegravir and dolutegravir have been compared to efavirenz in PWH with tuberculosis, but to date, no phase III randomized trial showed the non-inferiority of INSTI-based regimens compared to efavirenz-based regimens [1,2].

In the ANRS 12180 Reflate TB phase II non comparative trial, that enrolled 153 French and Brazilian patients, raltegravir 400 twice daily, raltegravir 800 twice daily or efavirenz had similar virologic efficacy at week 48 [3,4]. In the ANRS 12300 Reflate TB2 phase III trial, enrolling 460 patients from 5 different countries, non-inferiority of raltegravir 400 twice daily compared to efavirenz was not demonstrated [2]. Overall success rates were lower than expected. Male sex, lower adherence to ART, and high baseline HIV-1 RNA were associated with virologic failure, and adherence was associated with pill burden, which likely explains trial results by lower adherence to the raltegravir twice daily regimen [5,6].

Stratified results by country from the Reflate TB2 trial indicated that raltegravir virologic outcomes might be better in Brazilian patients. To further understand if virologic outcomes differed between countries and to compare raltegravir and efavirenz-based regimens in a larger population, we pooled data from the ANRS 12180 Reflate TB and ANRS 12300 Reflate TB2 trials. We sought to analyze virologic success rates in each country and determine factors associated with virologic success.

METHODS

We performed a pooled analysis of two randomized clinical trials evaluating raltegravir (400 mg twice daily) and efavirenz 600mg once daily for the treatment of HIV-1 infection in PWH treated for tuberculosis, the ANRS 12180 Reflate TB and the ANRS 12300 Reflate TB 2 trials. For the present study, we excluded patients from France (n=12) due to their low number that would not allow for comparisons with other countries. We also excluded participants from the ANRS 12180 Reflate TB

phase II study who were randomized to the raltegravir 800 mg twice daily arm. Detailed design of the two trials have been published previously [2,3]. Inclusion and exclusion criteria for both trials were similar (supplementary appendix). In brief, ART naïve PWH treated with standard anti-tuberculosis treatment in Brazil (Reflate TB and Reflate TB2) and Côte d'Ivoire, Mozambique and Vietnam (Reflate TB2) were randomized to initiate raltegravir- or efavirenz-based ART within the first 8 weeks of tuberculosis therapy.

Both study protocols were approved by relevant National and Local Ethics Committees in all participating countries and registered with ClinicalTrials.gov (NCT00822315 and NCT02273765). All participants provided signed informed consent before enrolment in the two trials.

In both trials we measured plasma HIV-1 RNA concentrations at weeks 0, 4, 12, 24, 32, 40, and 48, using the COBAS Taqman HIV-1 assay (version 2.0; Roche Diagnostics, Meylan, France) in Côte d'Ivoire, Mozambique, and Vietnam. In Brazil, the VERSANT HIV-RNA 3.0 assay (bDNA; Bayer, Berkeley, CA, USA) was used during the ANRS 12180 Reflate TB trial and Abbott RealTime HIV-1 was used during the ANRS 12300 Reflate TB2 trial.

Our primary outcome was the proportion of participants with virologic success at week 48 (plasma HIV-1 RNA <50 copies/mL, FDA Snapshot algorithm). Secondary outcomes were the proportion of virologic success using 200 and 1,000 copies/mL HIV RNA thresholds.

We compared patient characteristics across countries and treatment arms using Wilcoxon tests and chi-square, or Fisher's exact test as appropriate. We assessed determinants of virologic success using logistic regression, with the country as the main independent variable and other independent variables that we selected based on previous evidence and clinical relevance. We included in the multivariate model variables that were significantly associated to the dependent variable with a level of significance $p=0.25$ in univariate analysis. We derived the final model using a stepwise descending selection retaining all variables with a level of significance $p=0.05$. We compared raltegravir-based and efavirenz-based ART

regimens in terms of virologic success at 48 weeks using a non-inferiority approach by calculating the 95% binomial confidence interval (CI for the treatment difference (raltegravir minus efavirenz) and comparing its lower bound to a non-inferiority margin of -12%. We analyzed data with the SAS software (version 9.4M3).

RESULTS

We included 97 participants from the ANRS 12180 Reflate TB phase II trial and 453 participants from the ANRS 12300 Reflate TB 2 phase III trial in his analysis (Figure S1). Of the 550 participants, 140 were from Brazil, 170 from Côte d'Ivoire, 129 from Mozambique and 111 from Vietnam (Table 1). Their median CD4⁺ T-cell count was 107.0 (40.0 - 236.0) per cubic millimeter, and median plasma HIV-1 RNA 5.4 (4.9 - 5.7) Log₁₀ copies/mL; 168/547 (30.7%) participants had a HIV-1 RNA above 500,000 copies/mL.

Several baseline characteristics differed across countries (Table 1). The proportions of female participants were 25.0%, 54.7 %, 44.2% and 20.7% ($p<0.0001$), median CD4 count was 128.5/mm³, 104.0/mm³, 210.0/mm³ and 34.0/mm³ ($p<0.0001$), and median HIV RNA was 4.9 log₁₀, 5.6 log₁₀, 5.3 log₁₀ and 5.6 log₁₀ ($p<0.0001$) in Brazil, Côte d'Ivoire, Mozambique and Vietnam, respectively. The median time from TB treatment initiation to ART initiation was longer in participants from Brazil: 35 days (25-44.5) compared to 21.0 (16.0-29.0), 17.0 (14.0-21.0) and 21.0 (16.0-29.0) in Côte d'Ivoire, Mozambique and Vietnam, respectively ($p<0.0001$) and the median delay between HIV infection diagnosis and ART initiation was also longer in Brazil ($p=0.0021$).

Overall, 362/550 (65.8%) participants achieved virologic success at week 48. Virologic success rates differed between countries: 105/140 (75.0%) participants in Brazil, 99/170 (58.2%) in Côte d'Ivoire, 84/129 (65.1%) in Mozambique and 74/111 (66.7%) in Vietnam had HIV-1 RNA<50 copies/ml on allocated treatment ($p=0.0217$) (table 1, additional details in Supplementary table S1). The proportion of participants with HIV RNA<50 copies at each visit according to baseline HIV RNA levels is represented for each country in figure S2.

Overall, 177/277 (63.9%) patients treated with raltegravir and 185/273 (67.8%) patients treated with efavirenz had a plasma HIV-1 RNA <50 copies/mL at week 48 (Table S2). The difference in virologic success at week-48 between the raltegravir and efavirenz groups was -3.9% (-11.8%; 4.1%), thus meeting the criterion for non-inferiority.

In participants receiving raltegravir, the proportion of virologic success at W48 was 55/70 (78.6%), 48/86 (55.8%), 40/65 (61.5%) and 34/56 (60.7%) in Brazil, Côte d'Ivoire, Mozambique, and Vietnam, respectively (p=0.0247). In participants receiving efavirenz the proportion of virologic success at W48 was 50/70 (71.4%), 51/84 (60.7%), 44/64 (68.7%) and 40/55 (72.7%) in Brazil, in Côte d'Ivoire, in Mozambique, and in Vietnam, respectively (p=0.3931).

At week 48, 397/550 (72.2%; 95%CI 68.4%-75.9%) participants had HIV-1 RNA <200 copies/mL and 407/550 (74.0%; 95%CI 70.3%-77.7%) participants had HIV-1 RNA <1,000 copies/mL.

The country, CD4 counts, and baseline HIV-1 RNA were associated to virologic success at week 48 in the univariate analysis. In the multivariate analysis, only baseline HIV-1 RNA (reference HIV-1 RNA \geq 500,000 copies/mL, HIV-1 RNA <100,000 copies/mL OR: 3.12 (95%CI 1.94; 5.01) and HIV-1 RNA 100,000-499,999 copies/mL OR: 1.80 (95% CI 1.19; 2.73)) and not the country remained independently associated with virologic success (Table 2).

DISCUSSION

In this pooled analysis of the ANRS 12180 Reflate TB phase II and ANRS 12300 Reflate TB2 phase III trials, baseline HIV-1 RNA and virologic success rates varied between countries. In Brazil, 75.0% of the participants achieved virologic success, which is 10 percent higher than in participants from Mozambique and Vietnam. The lowest virologic success rate was observed in Côte d'Ivoire, with only 58.2% of the participants achieving virologic suppression. Differences in success rates by country were driven by differences in baseline HIV-1 RNA. In Brazil, only 14.3% of participants had baseline HIV-1 RNA >500,000 copies/mL compared to 28.7 to 41.1% in the other three countries.

Other factors may contribute to the differences in virologic success rates observed between countries including low CD4 counts, HIV pretreatment resistance, HIV-1 viral subtypes, and adherence to ART [7–9]. CD4 counts differed between countries but our results do not show that participants with lower CD4 counts were those with the lowest virologic success rates. Indeed, participants from Vietnam had median CD4 counts below the threshold of 50 cells/mm³, but they had similar median baseline HIV-1 RNA and higher success rates than participants from Côte d’Ivoire who had higher baseline CD4 counts. We did not assess baseline primary resistance to ART or HIV-1 subtypes and whether they could also explain the differences in baseline HIV-1 RNA or virologic outcomes between countries, but this study is ongoing. Previous studies found that HIV-1 non-B subtypes, more prevalent in Africa and Asia, might be associated with virologic failure [9,10]. HIV-1 subtype diversity has also been associated with the development of resistance to integrase inhibitors [11]. Viral load assays used in the two trials are known to correctly estimate the specific subtypes of each country and it is unlikely that differences between countries could be driven by underestimation or overestimation of baseline viral load [12]. Whether viral subtypes could explain higher baseline HIV-1 RNA at baseline and influence disease progression is not clear from previous reports [13]. We could not evaluate if differences in patient management could explain the differences observed between countries, nor could we compare adherence using pill count ratio between the four countries, which constitute limitations of our study.

We confirmed in a large cohort that lower HIV-1 RNA at baseline was independently associated with virologic suppression at week 48. Our previous secondary analysis of the ANRS 12300 Replate TB2 trial showed that sex, baseline HIV RNA and adherence measured by pill count ratio, were all predictors of virologic success but we were not able to measure differences related to country [5]. In this pooled analysis, non-inferiority of raltegravir was demonstrated compared to efavirenz, which contrasts with the results of the phase III trial. Merging data from the phase II study increased the number of Brazilian participants who had lower HIV-1 RNA at baseline, and this might have reduced the difference between treatment groups arms.

In conclusion, in this large cohort pooling data from two randomized trials evaluating standard dose raltegravir and standard dose efavirenz in LMICs for the treatment of PWH with TB, we found baseline HIV-1 RNA and rates of virologic success at week 48 differed between countries. Overall, raltegravir was non-inferior to efavirenz but success rates were lower than expected, and the main factor associated with virologic success was lower baseline HIV-1 RNA. Importantly, none of the countries reached the UNAIDS target of 95% virologic suppression in PWH accessing ART, with only 74.0% of participants overall achieving HIV-1 RNA <1,000 copies/mL. Data is lacking regarding virologic outcomes with dolutegravir, the now recommended first line ART for PWH treated for TB in LMICs. Large cohorts within national programs should provide more data on INSTIs use in the context of HIV/TB co-infection and better understand country differences.

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NDC, OM, CC conceived and designed the study. NDC, OM, LW, BG contributed to the interpretation of the results. CB, EM, CK, GDC, JP, BG, NDC, LW, OM, DD, JMM implemented the trials and enrolled participants. CC did the statistical analysis. CC, OM prepared the report. NDC wrote the first draft and all authors reviewed and approved the final version of the report and the manuscript.

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Data sharing statement

Data will from this study will not be shared publicly. Data could be made available by the sponsor (ANRS) to any researcher interested in getting the Reflate-TB2. Deidentified participant data would be made available with a data dictionary and shared under a data Transfer Agreement. Data can be requested at the following email address: nathalie.de-castro@aphp.fr.

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Table 1. Characteristics of patient at baseline and virologic success at week 48 by country

	N*	TOTAL (N=550)	N*	Brazil (N=140)	N*	Côte d'Ivoire (N=170)	N*	Mozambique (N=129)	N*	Vietnam (N=111)	p
Female sex		208 (37.8)		35 (25.0)		93 (54.7)		57 (44.2)		23 (20.7)	<.0001
Age (years)		35.4 (29.0 - 43.0)		35.2 (29.0 - 43.9)		38.0 (33.0 - 44.9)		37.0 (29.4 - 42.4)		28.9 (25.4 - 34.2)	<.0001
BMI (Kg/m²)	548	19.4 (17.6 - 21.4)	139	21.0 (19.1 - 22.7)	169	19.4 (17.8 - 21.4)		19.2 (17.8 - 20.7)		17.7 (16.0 - 19.4)	<.0001
CD4 (/mm³)	549	107.0 (40.0 - 236.0)		128.5 (50.0 - 226.5)	169	104.0 (47.0 - 229.0)		210.0 (88.0 - 362.0)		34.0 (14.0 - 65.0)	
≤50	549	173 (31.5)		33 (23.6)	169	49 (29.0)		20 (15.5)		71 (64.0)	<.0001
]50 - 200]	549	201 (36.6)		62 (44.3)	169	68 (40.2)		41 (31.8)		30 (27.0)	
]200 - 500]	549	175 (31.9)		45 (32.1)	169	52 (30.8)		68 (52.7)		10 (9.0)	
HIV-1 RNA (log₁₀ copies/mL)	547	5.4 (4.9 - 5.7)		4.9 (4.4 - 5.5)	168	5.6 (5.2 - 5.9)		5.3 (4.9 - 5.8)	110	5.6 (5.1 - 5.9)	
<100 000 copies/mL		167 (30.5)		75 (53.6)	168	31 (18.5)		43 (33.3)	110	18 (16.4)	<.0001

	N*	TOTAL (N=550)	N*	Brazil (N=140)	N*	Côte d'Ivoire (N=170)	N*	Mozambique (N=129)	N*	Vietnam (N=111)	p
[100 000 - 500 000[copies/mL		212 (38.8)		45 (32.1)	168	68 (40.5)		49 (38.0)	110	50 (45.5)	
≥ 500 000 copies/mL		168 (30.7)		20 (14.3)	168	69 (41.1)		37 (28.7)	110	42 (38.2)	
Time since first HIV + test (days)	548	25.5 (16.0 - 41.5)		50.0 (32.5 - 84.5)		28.0 (19.0 - 40.0)	128	19.0 (15.0 - 22.0)	110	16.0 (7.0 - 27.0)	0.0021
Time on TB treatment at W0 (days)		21.0 (16.0 - 33.0)		35.0 (25.0 - 44.5)		21.0 (16.0 - 29.0)		17.0 (14.0 - 21.0)		21.0 (16.0 - 29.0)	<.0001
Tuberculosis presentation											
Pulmonary tuberculosis		355 (64.5)		68 (48.6)		99 (58.2)		122 (94.6)		66 (59.5)	<.0001
Extra pulmonary tuberculosis		96 (17.5)		12 (8.6)		54 (31.8)		7 (5.4)		23 (20.7)	
Pulmonary + extrapulmonary tuberculosis		99 (18.0)		60 (42.9)		17 (10.0)		0.0 (0.0)		22 (19.8)	
Virologic success (HIV-1 RNA <50 copies per mL)		362 (65.8)		105 (75.0)		99 (58.2)		84 (65.1)		74 (66.7)	0.0217
Virologic non-response		132 (24.0)		21 (15.0)		47 (27.6)		34 (26.4)		30 (27.0)	
No data in the week 48 window		56 (10.2)		14 (10.0)		24 (14.1)		11 (8.5)		7 (6.3)	

Data are n (%) or median (IQR). †Body-mass index is the weight in kilograms divided by the square of the height in meters

Table 2: Factors associated with VL<50 copies at W48

	Total N	Virologic success N (%N) or median (q1 q3)	Univariate analysis				Multivariate analysis			
			OR	Lower 95% CI	Upper 95% CI	Pr > Chi- Square	OR	Lower 95% CI	Upper 95% CI	Pr > Chi- Square
Treatment										
Efavirenz	273	185 (68%)	1			0.3393				
Raltegravir	277	177 (64%)	0.84	0.59	1.20					
Country										
Brazil	140	105 (75%)	1			0.0233				
Ivory Coast	170	99 (58%)	0.46	0.29	0.76					
Mozambique	129	84 (65%)	0.62	0.37	1.05					
Vietnam	111	74 (67%)	0.67	0.38	1.16					
Sex										
Male	342	216 (63%)	1			0.0922				
Female	208	146 (70%)	1.37	0.95	1.99					
Age										
>35	280	189 (68%)	1			0.3972				
≤35	270	173 (64%)	0.86	0.60	1.22					
Baseline BMI										
> 18.5	340	234 (69%)	1			0.0632				
≤18.5	208	127 (61%)	0.71	0.50	1.02					
Baseline CD4 T cell count (/mm³)										
<50	173	105 (61%)	1			0.0382				
50 to 199	201	128 (64%)	0.88	0.58	1.34					
≥200	175	128 (73%)	0.57	0.36	0.89					
Baseline HIV-1 RNA (copies/mL)										
≥500,000	168	89 (53%)	1			<.0001				<.0001
<100,000	167	130 (78%)	3.12	1.94	5.01		3.1 3	1.95	5.03	
100,000 to 499,999	212	142 (67%)	1.80	1.19	2.73		1.8 5	1.22	2.81	

10 General discussion

To address challenges faced in the co-treatment of HIV infection and TB, we need drugs that are well tolerated and have high efficacy rates to treat both infections, without drug-drug interactions. When the Reflate TB 2 trial was designed, efavirenz-based ART regimens were the only options for patients with tuberculosis. Given the tolerance and drug-drug interaction profiles of raltegravir, we felt that the availability of this drug might offer an opportunity for co-treatment of TB and HIV. At the time, raltegravir was the only INSTI available for HIV infection treatment.

The ANRS 12 180 Reflate TB and ANRS 12 300 Reflate TB2 trials, as well as the secondary analysis presented in this thesis provide unique data on INSTI-based ART in the context of HIV/ TB co-infection. The 15 year-long processes followed all evaluation steps for new antiretroviral strategies, starting with a phase II study including a PK evaluation, followed by a validation phase III trial and additional secondary analyses. The overall aim was to validate the use of raltegravir in a new indication for ART naïve patients with TB. This collaborative trial also created the opportunity for a new cooperation between five countries on four different continents within the ANRS|MIE sites network, and has paved the way for other multi-country ANRS|MIE trials.

Raltegravir, as alternative in PWH treated for tuberculosis with rifampicin-based TB treatment.

In the ANRS 12300 Reflate TB 2 trial, we did not demonstrate non-inferiority of a raltegravir based antiretroviral regimen compared with an efavirenz-based regimen in terms of virological suppression at week 48 in ART-naïve PWH with TB. We found that participants with baseline HIV-1 RNA < 100,000 copies/mL at baseline had 75% rates of virologic success in the raltegravir arm and 71% in the efavirenz arm compared to 45% and 61% for those with baseline HIV-1 RNA \geq 500,000 copies/mL. There was a grading in the difference in virologic success rates between the two arms, with a 4% difference in favour of raltegravir for the < 100,000 copies/mL strata, a 3 % difference in favour of efavirenz in the 100,000 to 499,000 copies/mL strata, compared to a 14% difference in favour of efavirenz in the \geq 500,000 copies/mL strata. This suggested the role of high baseline HIV viral load as an explaining factor for virologic non response in both arms, but more pronounced in the raltegravir arm.

The lower-than-expected success rates at week 48 (less than 70%) was not expected based on previous virologic and PK data from clinical trials on raltegravir efficacy. Indeed, efavirenz and raltegravir are known to have similar virologic efficacy and low genetic barrier to resistance. PK data from the phase II 12 180 Reflate TB study had shown that the lower concentrations of raltegravir did not impact virologic efficacy of raltegravir [156,191]. Moreover, the proportion of emerging resistance to raltegravir or efavirenz in the ANRS 12 300 Reflate TB 2 trial did not support that resistance was the explanation for the difference between arms. At virologic failure, there were higher rates of resistance

to efavirenz (69%) than to raltegravir (38%). When looking at virologic suppression with the 200 copies/mL thresholds, success rates were 69% and 72% in the raltegravir and efavirenz arms, respectively, which was also lower than expected [156].

The context has changed since we conducted both the ANRS 12180 Reflate TB and the ANRS 12300 Reflate TB 2 trials. Second generation INSTIs are now the preferred options in all countries as part of single tablet regimens. The WHO recommends dolutegravir in LMICs for all patients, with the need to add a supplementary tablet of dolutegravir 50 mg for patients with tuberculosis [123]. Raltegravir is no longer part of the preferred first line options to treat HIV infection in high income countries, but is part of recommended alternative regimens in Europe and the USA [102,127]. We believe, based on the results presented in this thesis, that in patients with HIV-1 RNA <100,000 copies/mL raltegravir provides good virologic efficacy and can be used as part of ART to treat PWH with TB. Data from small real-life studies also suggest that raltegravir can be used, although in such studies ART is often switched to a more convenient once daily single tablet regimen after the end of TB treatment, making comparisons difficult with results from the Reflate TB 2 trial [201,202]. In a retrospective French cohort study enrolling 117 patients, raltegravir and dolutegravir had similar efficacy and safety results compared to efavirenz for the treatment of PWH with TB [202]. Success rates at week 48 were 61.5%, 63.2% and 69.5% in the raltegravir, dolutegravir and efavirenz groups, respectively, but numbers were small in each treatment group [210]. In European and US guidelines, efavirenz remains the preferred option for HIV/TB co-infection, and based on the results of both Reflate TB and Reflate TB2 trials, raltegravir was incorporated as an alternative to efavirenz, at the same level as double dose dolutegravir in the European guidelines [102,127].

Pre-treatment HIV viral load, the main driver of antiretroviral treatment efficacy in PWH with advanced disease

In our analysis of factors associated to virologic success, we found that baseline HIV-1 RNA was the strongest predictor of virologic success. Participants with a baseline HIV-1 RNA <100,000 copies/mL had higher odds of achieving virologic success compared to those with HIV RNA \geq 100,000 copies/mL. Higher level of HIV-1 RNA at ART initiation was also found to be associated with virologic failure in the NAMSAL study, another randomized trial conducted in Cameroon in PWH without TB that compared dolutegravir and efavirenz-based ART [211]. Conversely, pivotal trials evaluating efavirenz, raltegravir or dolutegravir in asymptomatic PWH showed that virologic efficacy was not affected by baseline viral load levels [186,193,196]. In the STARMRK pivotal trial conducted between 2006 and 2008 that compared raltegravir to efavirenz, the proportion of participants with HIV-1 RNA < 50 copies/mL at week 48 was more than 80% in both arms and efficacy rates were not different according to baseline HIV-RNA levels (55% of the participants had HIV-1 RNA >100,000 copies/mL) [186]. We expected to find that lower CD4 counts, a marker of advanced disease, would also be associated with

virologic failure but as 70% of the participants had CD4 counts $<200/\text{mm}^3$, this was probably a limitation to find an association between CD4 counts and virologic outcomes.

The discrepancy observed in the results of the phase II Reflate TB and phase III Reflate TB2 trials raised the question of the contribution of the country of origin to explain part of the differences observed between Brazilian participants and those from the other countries. Indeed, in the phase II ANRS 12180 Reflate TB trial, 95% of the participants were from Brazil, whereas in the Reflate TB 2 trial, there were only 9% of Brazilian participants, with 65% and 24% African and South East Asian participants, respectively. In the 44 Brazilian participants enrolled in the ANRS 12300 Reflate TB2 trial, success rates were 17/21 (81%) and 15/22 (68.2%) on raltegravir and efavirenz, respectively which contrasted with the results from other countries. The lower number of Brazilian participants did not allow for strong comparisons between countries. Pooling the data from the two trials allowed us to analyse more than 100 participants per country (excluding the few French participants). This analysis confirmed that baseline HIV-1 RNA was the main factor influencing virologic success and that this was the driver of differences between countries in virologic success rates. Indeed, Brazilian participants had significantly lower median HIV-1 RNA at baseline compared to participants from other countries. This finding remains to be explained. We could not evaluate if differences in patient management could explain the differences observed in virologic outcomes at week 48. For example, the capacity to hospitalize more severe patients, health care staffing or adherence counselling/monitoring might have been different between the study sites.

In our pooled analysis 70% of the participants achieved HIV-1 RNA $<1,000$ copies/mL, which is far from the UNAIDS target of 95% of people on ART achieving virologic success [212]. These lower-than-expected success rates are a concern as most countries are committed to meet the UNAIDS 95-95-95 targets in the HIV cascade by 2025. In 2021, 85% of PWH knew their HIV status, among people who knew their status 67% were accessing ART and among people accessing treatment, 92% were virologically suppressed [212]. The last 95 of the UNAIDS targets seems indeed attainable in the context of the use of dolutegravir, a potent drug with low risk of emergence of resistance. In fact, in light of the results from non-inferiority trials evaluating INSTIs conducted in the past 10 years where success rates of INSTI-based ART were 90%, the goal seemed at hand [193,194,196,203,213–215]. However, in these trials, the median HIV-1 RNA at baseline was usually less than 5 log copies/mL (around 4.5 log copies/mL for the majority) with more than 80% of the participants having baseline HIV-1 RNA $<100,000$ copies/mL. Similarly, in the ADVANCE trial conducted in 2017 and 2018 in Africa, success rates at week 48 were 84-85% on dolutegravir-based ART and 79% on efavirenz-based ART, but participants had median CD4 counts of $317/\text{mm}^3$ and 78% had baseline HIV-1 RNA $<100,000$ copies/mL [194].

The evolution of the characteristics of participants in clinical trials evaluating INTSIs is explained by the evolution of treatment guidelines based on CD4 counts at ART initiation that evolved over the past 10 to 15 years. Until 2007-2009, ART was recommended only in PWH with CD4 counts less than 200/mm³, treatment was then recommended if CD4 counts were less than 350/mm³ and finally, universal treatment has been recommended since 2015. The population of the Reflate TB2 study was very different from that of most of the above-mentioned trials. Participants had TB as manifestation of advanced disease and 75% had HIV-1 RNA>100,000, one third had HIV-1 RNA>500,000 copies/mL. Our results confirm that PWH with tuberculosis must be considered as a specific sup-population who should benefit from targeted interventions to improve access to ART and virologic monitoring as they may hardly meet the last 95 of the UNAIDS target.

Adherence issues in PWH with advanced disease in LMICS

Our hypothesis was that lower adherence might have been an aggravating factor, combined with high levels of HIV-1 RNA at ART initiation. During the 48-week duration of the Reflate TB2 trial, a high number of participants had sub-optimal adherence to ART and adherence decreased between the two trial arms after the end of TB treatment. We assessed pill count adherence ratio as our main measure of adherence and described other components of adherence in the trial. Over the 48-week follow-up period, only 290/444 (65%) participants had an optimal adherence with pill count adherence ratio $\geq 95\%$. Indeed, we found that 43% of participants on raltegravir and 27% participants on efavirenz had ART adherence less than 95%. Participants with pill count adherence ratio $<95\%$ were also those with self-reported non-adherence. In the analysis of factors associated to virologic success, participants with pill count adherence ratio $\geq 95\%$ had more than twice the chance of achieving virologic success compared to those with adherence $<95\%$. Antiretroviral pill burden was the only predictor of poor adherence, and this was driven by the twice daily dosing of raltegravir based antiretroviral regimen.

The lower adherence in participants from the Reflate TB 2 trial, particularly after week 24 was an unexpected finding. The open label design of the phase III trial without placebo may have introduced bias and a difference in adherence between groups. We did not expect adherence issues as patients treated concomitantly for TB and HIV are already on a twice daily dosing for their medications with the need to take pills in the morning (TB drugs) and evening (efavirenz-based ART). We could not evaluate which instructions were given to the participants regarding drug intake. Participants were supposed to be instructed to take raltegravir with food, as stated in the protocol, to increase the absorption of the drug and minimize the effect of rifampicin on raltegravir PK. This could have favoured suboptimal adherence in the morning with the necessity to take TB drugs on a fasting state and raltegravir afterwards with food. We were not able to evaluate the time of drug intake to further explore this hypothesis. Adherence was also lower in the efavirenz arm after week 24, suggesting that other factors may be the drivers of adherence issues after the end of TB treatment.

It is usually accepted that adherence to 90 - 95% of treatment doses is sufficient to ensure good virologic control in patients on stable ART that are virologically suppressed [216–219]. This is especially the case when drugs with high genetic barrier to resistance are used as part of ART and when PK factors allow to maintain virologic suppression despite lapses in drug intake. This phenomenon is known as the forgiveness of ART regimens [220,221]. ART simplification trials bring interesting data with this regard in high income countries. The ANRS 170 QUATUOR trial, showed the non-inferiority of a strategy based on 4-consecutive-days-on and 3-days-off ART compared to taking continuous ART [222]. This means that in virologically suppressed patients, highly adherent to ART using a combination with high genetic barrier, taking only 60% of the doses over one week may not affect treatment efficacy in the short term. However, the situation is very different in patients initiating ART with more advanced disease, as shown in the NAMSAL and ANRS 12300 Reflate TB2 trials [209,223]. Monitoring of adherence and actions to support adherence during the first year of ART are critical in this period where PWH are starting the process of acceptance of HIV infection and ART as lifelong conditions.

Various indirect measures of adherence have been used, including patients' self-reports, pill count adherence or medication possession ratio, pharmacy refill, physician evaluation or electronic measures. There is no gold-standard and all have drawbacks, so the addition of different measures may be more robust than one single evaluation [216,224]. The most frequently used adherence measures are self-reported adherence or pill-count by the pharmacist. We used both in the ANRS 12300 Reflate TB2 trial. Adherence can vary for many reasons and a perfectly adherent person can have lapses in treatment intake anytime during follow-up. With the advent of once daily highly active and well tolerated antiretroviral therapy combinations, adherence to treatment has improved, leading to less concerns about the emergence of resistance or virologic failure. However, the Reflate TB2 and the NAMSAL trials have shown that adherence issues combined with high baseline viral loads levels may be an issue in PWH with advanced disease, even with dolutegravir containing regimens. Interestingly, we found that pill count adherence ratio measured at the pharmacy level, could help to identify patients at higher risk of virologic failure. Although it is not a perfect measure of the real adherence, it is possible to use in programmatic conditions and may allow to identify sooner patients who need closer clinical or virological monitoring. With the possibility to perform close virologic monitoring in high income countries, other measures of adherence were less and less used, especially since the availability of daily single pill regimens. The best measure of adherence may be HIV-1 viral load but in most national programs from LMICs, during the first year of ART, HIV viral load is usually measured only once or twice. The consequence is that it may take a few months to identify patients with ongoing viraemia and subsequent risk of emergence of resistance. In this context, it is crucial to monitor adherence at least at each visit to the clinic with simple although imperfect tools. The physician's evaluation, along with self-adherence questionnaires or treatment accountability at the pharmacy can be combined.

Implications of our research for twice daily dosing of dolutegravir to treat PWH with TB

The results of the phase III Reflate TB2 trial are important and need to be interpreted in the international context of the latest recommendation to use another INSTI, dolutegravir, in low- or middle-income countries as first line option for HIV/TB co-infection. Indeed, although dolutegravir and raltegravir are very different drugs, the questions raised by this thesis regarding the consequences of lower adherence in PWH with high baseline HIV-1 RNA may also apply to dolutegravir. Both drugs need to be taken twice daily when co-administered with rifampicin and have similar drug-drug interactions with rifampicin. Dolutegravir has been now rolled out in most LMICs as part of a single tablet regimen co-formulated with two NRTIs [225]. It has a better tolerance profile and is more robust with higher barrier to resistance and forgiveness. In LMICs where resistance monitoring is difficult, these are important advantages, and this explains why dolutegravir replaced efavirenz. The observation that the twice daily dosage of raltegravir might have been a disadvantage in the Reflate TB 2 trial raises concerns about the twice daily dosage of dolutegravir in the same context of HIV/TB co-infection. To date, available data from non-comparative clinical trials or real-life cohorts from national programs are limited regarding dolutegravir efficacy when co-administered with rifampicin [157,199,200]. In PWH already virologically suppressed with the standard dose dolutegravir as part of a single tablet regimen, the risk of lower adherence and its impact on virologic control may not be the same as for those with advanced disease initiating ART-based dolutegravir. The RADIANT study, also a small non comparative trial, showed standard dose dolutegravir resulted in similar efficacy rates than double dose dolutegravir in South Africa in PWH treated for TB, but these data need confirmation [158]. There is a risk of emergence of resistance in case of suboptimal dosages of dolutegravir with potential ongoing viral replication. This needs to be monitored carefully within national programs.

One other question is how the expected evolution of TB treatment will influence the interactions with ART. Treatment of drug sensitive TB is evolving towards shorter 4 months treatments with rifapentine and moxifloxacin. If TB treatment is shorter, the duration of the interaction between rifamycins and ART will also be shorter, with a lower risk of suboptimal dosages of ART drugs and also lower risk of sub-optimal adherence due to pill burden. However, the shorter regimen has not been evaluated in PWH with advance disease and/or disseminated TB. This is an important caveat for its roll-out in countries with high rates of HIV and TB co-infection. Moreover, rifapentine is also a potent inducer of hepatic cytochromes and other metabolic pathways so the interactions with antiretroviral drugs remain a concern. PK studies conducted in the context of TPT have shown that dolutegravir exposition remained in acceptable ranges when co-administered at the standard 50 mg once daily dosage with once weekly rifapentine [226]. This needs to be confirmed when higher doses of rifapentine are used for TPT (1HP) or for the treatment of active TB. With more TB drugs involved and higher rifapentine doses, the magnitude of the interaction may be different.

Data from clinical trials support that efavirenz remains the best options for PWH with TB

In the context of HIV/TB co-infection, to date, efavirenz-based ART remains the best treatment if we look at virologic outcomes and no other option has been validated in a non-inferiority trial. INSTI-based regimens, despite high anti-viral efficacy in patients without tuberculosis, have lower rates of virological suppression at week 48 than efavirenz-based regimens in patients with tuberculosis [157,209]. The ANRS 12300 Reflate TB 2 trial is one of the few phase III non-inferiority trials evaluating virologic efficacy of ART in PWH with TB and the only non-inferiority trial to evaluate an INSTI-based regimen in this context. The virologic endpoint chosen in the Reflate TB 2 trial followed the Food and Drugs Administration (FDA) guidance for industry, the gold standard with regards to evaluation of new antiretroviral drugs [208]. To our knowledge, only the ANRS 12146 CARINEMO trial, another non-inferiority trial published in 2013, had a similar virologic endpoint at week 48 (missing data or treatment interruption = failure) and evaluated nevirapine compared to efavirenz [146]. Most of the randomized trials conducted in the context of rifampicin-based TB treatment were not designed to evaluate virologic endpoints nor were powered to evaluate non-inferiority compared to efavirenz, the standard of care until 2018 when dolutegravir was recommended by the WHO.

The contradictory results from the ANRS 12180 Reflate TB and 12300 Reflate TB 2 trials highlight that findings from non-comparative studies may not be generalizable and that confirmatory phase III trials remain key to validate new ART options, although it is a long and complex process. Indeed, conducting clinical trials in PWH with advanced disease in LMICs is a challenge. It's long, costly and also depends on the industry to have access to new drugs. This is well illustrated by the fact that only two non-inferiority phase III trials were completed to date in the field of HIV/TB co-infection (one other trial from India had to be discontinued prematurely) [146,209]. Notably, both the ANRS 12146 CARINEMO and ANRS 12300 Reflate TB 2 trials evaluated twice daily regimens. These two trials failed to show the non-inferiority of twice daily nevirapine or raltegravir compared to once-daily efavirenz in late-presenters with high baseline HIV-1 RNA. Our results also highlight the importance of using a placebo when adherence issues are expected, especially when comparing two regimens with different daily dosing. As a consequence, this long and complex process discourages the conduct of large trials for virologic evaluation of new ART regimens in patients with advanced disease.

That said, conducting phase II studies followed by phase III non-inferiority trials is long process and will show results after 5 to 10 years. One other issue is the use of the FDA snapshot algorithm with very stringent criteria in a situation where a substantial proportion of people die or change ART for reasons other than virologic failure. In the Reflate TB 2 trial, this represented 15% of the participants. On the other hand, to provide robust guidelines we need evaluations from phase III trials, especially when there are drug-drug interactions between ART and TB treatments or other factors that might not be identified in smaller non comparative exploratory studies, as it was the case in the ANRS 12180 Reflate TB trial.

With dolutegravir availability in national HIV programs, it is unlikely that a large phase III trial will be conducted to compare dolutegravir to efavirenz in PWH with TB. There is an urgent need to analyse and publish data from existing cohorts and national programs to evaluate virologic outcomes in real life settings.

Perspectives: evaluation of INSTI-based therapy in Brazil and West Africa

In Brazil, universal HIV care and ART are free of charge since 1996 through the Unified Health Care system (SUS) and HIV testing for patients with TB has been recommended since 1998. TB diagnosis and treatment are also free of charge through the SUS. In 2021, 76.9% of all persons with TB diagnosed in the country were tested for HIV (compared to 82.8% in 2018 and 2019, before the COVID-19 pandemic). Overall, there were 5,652 (8.3%) PWH among all TB cases (compared to more than 8,000 in the pre-pandemic era). In 53.3% of these 5,652 new PWH with TB, TB and HIV infection were diagnosed concomitantly. The number PWH diagnosed with TB decreased in 2020 and 2021 but it was stable between 2015 and 2019, meaning that 3,000 to 3,500 ART-naïve PWH with TB are eligible for ART annually in Brazil since 2015.

Efavirenz (in association with tenofovir and lamivudine) was the preferred option to treat PWH with TB in Brazil up to 2018. Based on the results of the ANRS 12 180 Reflate TB phase II study, the Brazilian ministry of Health issued the recommendation to replace efavirenz with raltegravir 400 mg twice daily in 2017 for severely immunosuppressed patients ($CD4 < 100 \text{ mm}^3$ or other opportunistic infection) or for patients with disseminated TB. Thus, ART naïve PWH, received one of these 2 options in 2017 and 2018. Since 2018, efavirenz was progressively replaced by dolutegravir for all PWH initiating ART, including those with tuberculosis who received double dose dolutegravir as per WHO guidelines.

We plan to analyse data from the national Brazilian HIV and TB programs to provide data on virologic efficacy of raltegravir, dolutegravir and efavirenz in PWH with TB since 2016. Brazil has implemented several data bases for the follow-up of the HIV and TB epidemics. The databases will be linked with the objective to identify the greatest number of cases, thus reducing possible underreporting and/or delay in data recording on the systems. This will enable to identify a cohort of all new PWH with TB identified through both TB and HIV/AIDS national surveillance programs between 2016 and 2021. In the final cohort of new PWH with TB we will be able to identify those receiving ART and select those treated either with efavirenz, dolutegravir or raltegravir. Mortality data as well as virologic outcomes will also be available. All data will be anonymized for the analysis.

We also plan to study virologic outcomes and adherence in PWH treated for tuberculosis within the prospective cohort nested within the International epidemiology Databases to Evaluate AIDS (IeDEA) West Africa. IeDEA collects observational data since 2006 in 44 countries from 7 geographic regions:

Asia-Pacific, the Caribbean, Central and South America region, Central, East, Southern, and West Africa regions, and North America. The IeDEA West Africa TB/HIV cohort is a prospective, observational, non-interventional study enrolling PWH with confirmed TB and receiving ART. Virologic outcomes will be assessed in PWH receiving dolutegravir based ART one year after TB treatment initiation as well as adherence using questionnaires and pill accountability.

With regards to HIV-1 RNA monitoring, in many programmatic settings, HIV-1 RNA may not always be measured at ART initiation. Moreover, HIV-1 RNA evaluations within the first year of treatment are very different from follow-up in clinical trials, with only one or two HIV-1 RNA measurements available for most patients. This is a limit when looking at virologic efficacy within the first year of ART. Different virologic endpoints than the usual virologic efficacy at week 48 are proposed. One is to define virologic success using the first undetectable HIV-1 RNA within the first year. This may underestimate the number of people quitting ART after a few months if patients are evaluated early (after 3 or 6 months) after starting ART with no other evaluation within the first year. Another option is to define a W48 window (for example W36 to W96) to have a better evaluation of virologic success rates after at least 9 months of ART. We plan to use this criterion in the analysis in the national Brazilian programs and in the IeDEA West Africa TB/HIV cohort but the feasibility will be evaluated in light of the proportion of missing data.

Conclusion

In PWH with tuberculosis initiating antiretroviral therapy in low-resources settings, advanced HIV disease with high baseline HIV-1 RNA hampers virologic success rates at one year. In this context optimal adherence is essential to maximize virological outputs and reduce the risk of failure and potential emergence of resistance to ART. Efavirenz-based regimens remain undefeated in non-inferiority trials evaluating ART combinations to treat HIV infection in PWH with TB. Based on the results presented in this thesis, raltegravir appears to be an acceptable alternative but only in selected patients, with baseline HIV-1 RNA below 100,000 copies/mL, fully adherent to their ART regimen, especially if raltegravir is used only for the duration of TB treatment.

We need to continue to evaluate new ART combinations for PWH with TB in phase III trials, especially with the advent of new ART formulations as long-acting injectables and new TB treatments. In the meanwhile, data from large cohorts in LMICs should provide insights on the efficacy of dolutegravir-based ART, the now standard of care as per WHO guidelines in LMICs. There is a need to improve HIV-1 RNA monitoring within the first year of ART to identify virologic failure as soon as possible, especially in PWH presenting with advanced disease that might need specific interventions to support adherence.

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Appendices

Appendix 1: Grinsztejn et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis* 2014;14:Articles

Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial



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Summary

Background Concurrent treatment of HIV and tuberculosis is complicated by drug interactions. We explored the safety and efficacy of raltegravir as an alternative to efavirenz for patients co-infected with HIV and tuberculosis.

Methods We did a multicentre, phase 2, non-comparative, open-label, randomised trial at eight sites in Brazil and France. Using a computer-generated randomisation sequence, we randomly allocated antiretroviral-naïve adult patients with HIV-1 and tuberculosis (aged ≥ 18 years with a plasma HIV RNA concentration of >1000 copies per mL) to receive raltegravir 400 mg twice a day, raltegravir 800 mg twice daily, or efavirenz 600 mg once daily plus tenofovir and lamivudine (1:1:1; stratified by country). Patients began study treatment after the start of tuberculosis treatment. The primary endpoint was virological suppression at 24 weeks (HIV RNA <50 copies per mL) in all patients who received at least one dose of study drug (modified intention-to-treat analysis). We recorded death, study drug discontinuation, and loss to follow-up as failures to achieve the primary endpoint. We assessed safety in all patients who received study drugs. This study is registered in ClinicalTrials.gov, number NCT00822315.

Findings Between July 3, 2009, and June 6, 2011, we enrolled and randomly assigned treatment to 155 individuals; 153 (51 in each group) received at least one dose of the study drug and were included in the primary analysis. 133 patients (87%) completed follow-up at week 48. At week 24, virological suppression was achieved in 39 patients (76%, 95% CI 65–88) in the raltegravir 400 mg group, 40 patients (78%, 67–90) in the raltegravir 800 mg group, and 32 patients (63%, 49–76) in the efavirenz group. The adverse-event profile was much the same across the three groups. Three (6%) patients allocated to efavirenz and three (6%) patients allocated to raltegravir 800 mg twice daily discontinued the study drugs due to adverse events. Seven patients died during the study (one in the raltegravir 400 mg group, four in the raltegravir 800 mg group, and two in the efavirenz group): none of the deaths was deemed related to study treatment.

Interpretation Raltegravir 400 mg twice daily might be an alternative to efavirenz for the treatment of patients co-infected with HIV and tuberculosis.

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Introduction

In patients with HIV, tuberculosis is the most common life-threatening opportunistic infection and is a leading cause of death. Concurrent treatment of HIV and tuberculosis decreases mortality,^{1–3} reduces tuberculosis relapse,⁴ and decreases community transmission of both tuberculosis and HIV.^{5,6} Antiretroviral treatment should, therefore, be started early in all patients with active tuberculosis, irrespective of their WHO clinical stage or CD4 cell count.⁷

However, despite the increasing number of antiretroviral drugs developed for the treatment of HIV infection, few options are available for patients co-infected with tuberculosis because of drug interactions. Rifampicin is the cornerstone of tuberculosis treatment, and is a potent inducer of hepatic cytochrome P450 3A4 enzymes, the main metabolic pathway of most non-nucleoside reverse

transcriptase inhibitors (NNRTIs) and protease inhibitors. Induction of these enzymes leads to increased clearance, reduced drug exposure, and potentially suboptimum clinical efficacy. Efavirenz, an NNRTI metabolised mainly through the cytochrome P450 2B6 pathway, also has pharmacokinetic interaction with rifampicin, which does not necessitate dose adjustment, and is the preferred antiretroviral to be used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) for the treatment of patients with both HIV and tuberculosis.⁷ Common side-effects of efavirenz are neuropsychiatric adverse events and rash, which can lead to treatment discontinuation.⁸ Additionally, primary NNRTI-resistance mutations could jeopardise the efficacy of efavirenz, and its use is controversial during the first trimester of pregnancy.^{9–11} Alternatives to efavirenz are therefore needed for the treatment of HIV in patients with tuberculosis.

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Raltegravir, a strand-transfer HIV integrase inhibitor, has shown potent antiviral activity and good tolerability in patients with HIV.¹² In the long-term follow-up of the phase 3 STARTMRK study in treatment-naïve patients,¹³ raltegravir had better virological and immunological efficacy and had a more favourable safety profile when compared with efavirenz. Raltegravir is not metabolised by the cytochrome P450 enzymes, but by uridine 5'-diphospho (UDP)-glucuronosyltransferase 1A1, an enzyme that is also induced by rifampicin. When raltegravir is given with rifampicin, and is used at the standard dose of 400 mg twice a day, findings from pharmacokinetic studies in healthy volunteers have shown a 40% decrease in plasma raltegravir area under the concentration-time curve, and a 61% decrease in plasma raltegravir trough concentration.¹⁴ Increasing the raltegravir dose to twice the standard dose (800 mg twice a day) compensates for the effect of rifampicin on the area under the concentration-time curve, although raltegravir trough concentrations remain 53% lower than expected.¹⁴ Therefore, both the US Food and Drug Administrations (FDA) and the European Medicines Agency approved the raltegravir package insert to recommend for raltegravir dosing to be increased from a standard 400 mg twice a day to 800 mg twice a day for patients taking concomitant rifampicin. Despite this recommendation, clinical experience with the combination of raltegravir and rifampicin is restricted, and the efficacy and safety of high-dose raltegravir during tuberculosis treatment has not been assessed.¹⁵⁻¹⁷ We assessed the efficacy and safety of two raltegravir doses in antiretroviral-naïve adults receiving rifampicin-based treatment for HIV and tuberculosis co-infection.

Methods

Study design and participants

The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) 12180 Reflate TB trial was a multicentre, randomised, parallel-group, phase 2, 48 week study, done at eight clinical sites, six in Brazil and two in France. We enrolled adult patients (aged 18 years or older) with previously untreated HIV-1 infection and a plasma HIV RNA concentration of greater than 1000 copies per mL, who had been receiving a rifampicin-based treatment for pulmonary or extrapulmonary tuberculosis for 2-8 weeks. Patients who had received previous antiretroviral treatment for less than 3 months (including single-dose nevirapine for prevention of mother-to-child transmission) were also eligible for inclusion, provided they had received antiretroviral treatment more than 6 months before enrolment, and that baseline HIV testing showed no mutations associated with resistance to NNRTIs, tenofovir, or lamivudine. Women who were pregnant (established by urinary pregnancy test) or breastfeeding were not eligible for inclusion, nor were those who

refused to use contraception (condom or intrauterine device) or those with HIV-2 infection, alanine aminotransferase concentrations of more than 2.5 times the upper limit of normal, bilirubin concentrations of more than five times the upper limit of normal, lipase concentrations of more than three times the upper limit of normal, creatinine clearance of less than 60 mL per min (Cockcroft formula), haemoglobin of less than 7 g/dL, absolute neutrophil count of less than 750 cells per μ L, platelet count of less than 50 000 per μ L, ongoing psychiatric disease, or any disorder (including, but not limited to, the consumption of alcohol or psychoactive drugs) that the enrolling clinician thought would compromise the safety of treatment or patients' compliance with the protocol. Individuals on concomitant treatment including phenytoin or phenobarbital (compounds interacting with UDP-glucuronosyltransferase 1A1) or who had prior tuberculosis infection with a rifampicin-resistant *Mycobacterium tuberculosis* strain were also not eligible. The upper threshold for alanine aminotransferase concentrations was lower in this study than in previous trials in HIV and tuberculosis co-infection (usually less than five times the upper limit of normal) to minimise the risk of liver toxicity because we were assessing a high dose of raltegravir with unknown safety.

All participants provided signed informed consent before or at the time of the screening visit. The protocol was approved by national and local ethics committees in Brazil (Comissão Nacional de Ética em Pesquisa [CONEP] and Comitê de Ética em Pesquisa [CEP] at IPEC/FIOCRUZ) and France (Comité de Protection des Personnes de Paris Ile de France I). We did this trial in accordance with Good Clinical Practices, the ANRS Ethical Chart for Research in Developing Countries, the Brazilian regulatory requirements for clinical trials, and the ethical principles of the Declaration of Helsinki.

Randomisation and masking

Using a computer-generated sequence, we randomly allocated eligible patients (1:1:1; stratified by country) to receive either raltegravir 400 mg twice a day, raltegravir 800 mg twice a day, or efavirenz as the standard of care. One trial statistician (Celine Colin, Reflate study group) generated the randomisation sequence, another (CG) did the analyses. This randomisation list was kept confidential to the site investigators. Randomisation was managed centrally at the clinical trial units at Institut National de la Santé et de la Recherche Médicale (INSERM) via the e-CRF (Capture System; Clinsight-Ennov, Paris, France). Treatment allocation was communicated to the site investigators sequentially, for consecutive enrolment of patients so that antiretroviral treatment could be started at the baseline visit with the assigned treatment. There was no masking in this study and we did not use a placebo to mask the raltegravir dose allocated to patients.

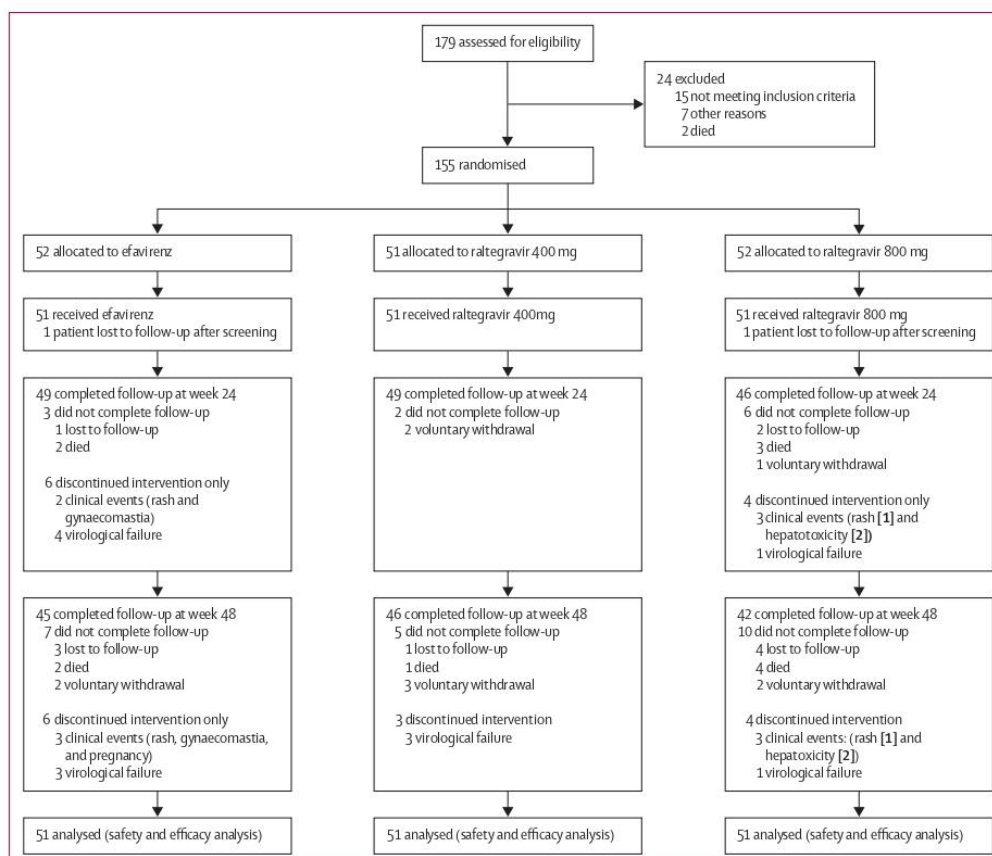


Figure 1: Trial profile

Procedures

All patients received a standard tuberculosis treatment regimen with WHO prequalified drugs on a fasting state with isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid and rifampicin for the subsequent 4 months. In case of renal, skeletal, or CNS tuberculosis, the duration of the maintenance regimen could be extended and the total duration of tuberculosis treatment in the trial was left to the investigator's discretion. Rifampicin was given at the dose of 10 mg per kg per day. Antiretroviral treatment was started after 2–8 weeks of tuberculosis treatment to allow enough time in the study for concomitant treatment with rifampicin and antiretroviral drugs.

Participants in the efavirenz group received 600 mg per day of efavirenz (one tablet), 300 mg per day of lamivudine (one 300 mg tablet in France, two 150 mg tablets in Brazil), and 245 mg per day of tenofovir disoproxil fumarate (one tablet). Patients were instructed to take all drugs at the same time with food, preferably at

bedtime, to reduce CNS adverse events with efavirenz. Patients in the raltegravir groups received either the standard dose of one 400 mg tablet twice a day, or the double 800 mg dose twice a day (two 400 mg tablets twice a day), in combination with 300 mg of lamivudine and 245 mg of tenofovir disoproxil fumarate. Patients were instructed to take raltegravir with food to increase its bioavailability. Efavirenz and lamivudine were provided by the Brazilian National HIV/AIDS Program. In France, efavirenz was obtained from Bristol Myers Squibb (Rueil Malmaison, France), and lamivudine from ViiV Health Care (Marly le Roi, France). Tenofovir disoproxil fumarate was donated by Gilead (Foster City, CA, USA), and raltegravir by Merck (Philadelphia, PA, USA), in both countries. Patients enrolled in the high-dose raltegravir group were required to switch to the standard dose of 400 mg twice a day of raltegravir 1 month after rifampicin discontinuation, but not before week 24. The protocol allowed substitution of tenofovir and lamivudine with other NRTIs in case of intolerance. Co-trimoxazole

prophylaxis was recommended for patients with CD4 counts less than 200 cells per μL .

We did clinical examination and laboratory analyses at screening and inclusion (baseline) visits, and at visits at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. Patients were diagnosed with confirmed or probable tuberculosis according to WHO guidelines for patients with HIV, and started tuberculosis treatment at clinics before referral to the trial site.¹⁸

Confirmed tuberculosis was defined by the detection of acid-fast bacilli in a sputum smear or a positive culture from a sputum sample, a lymph node aspirate, or a sample from another sterile site. Probable tuberculosis required a clinician's assessment that signs and symptoms warranted empirical tuberculosis treatment. Tuberculosis could be either pulmonary or extrapulmonary.

Smears and cultures from sputum or extrapulmonary specimens were done at the screening visit, if not already available. Chest radiographs were also done at the screening visit, unless already available at the time of the tuberculosis diagnosis. In patients with prior tuberculosis, resistance testing for rifampicin was done on available strains. During follow-up, sputum microscopy and chest radiographs were done, according to the national guidelines in each country, and at least week 12.

Hepatitis B (defined as detection of hepatitis B surface antigen) and hepatitis C (defined as detection of hepatitis C virus specific antibodies) infection status were assessed at the screening visit. HIV infection was confirmed at the screening visit by detection of HIV-specific antibodies by ELISA and western blot or immunofluorescence. We measured plasma HIV RNA concentrations with the COBAS Taqman HIV test (version 2.0; Roche Diagnostics, Meylan, France) in France, and the VERSANT HIV-RNA 3.0 assay (bDNA; Bayer, Berkeley, CA, USA) in Brazil. We assessed CD4 cell counts at baseline and all consecutive visits by flow cytometry.

We assessed the presence of resistance mutations to NRTIs, NNRTIs, and integrase inhibitors in patients with virological failure by sequencing the reverse transcriptase and integrase genes, and reporting mutations by use of the consensus technique of the ANRS AC11 Resistance Group, or the Trugene HIV-1 genotyping assay (Siemens Healthcare, Saint Denis, France), both at the time of confirmed virological failure and at baseline, using stored plasma specimens.

We measured full blood cell counts, alanine and aspartate aminotransferase, lipase, creatinine, alkaline phosphatase, and total bilirubin concentrations, and did urinary pregnancy tests at screening visits and at each follow-up visit for women of childbearing potential. Fasting glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides were measured at baseline and weeks 12, 24, and 48.

We monitored adherence to antiretroviral drugs using the ANRS self-report adherence questionnaire based on a 4 day recall period before the visit. We assessed the intensity of adverse events by the ANRS Scale for Grading Adult Adverse Events (grade 1 defined as mild, grade 2 as moderate, grade 3 as severe, and grade 4 as life-threatening).¹⁹ We defined serious adverse events as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, needed hospital admission or an extended hospital stay, resulted in disability or incapacity, or resulted in a congenital abnormality or birth defect. We also regarded grade 3 or 4 clinical and laboratory adverse events as serious adverse events.

Outcomes

The primary outcome was the proportion of patients with a plasma HIV RNA below 50 copies per mL at week 20, confirmed at week 24, with missing data and treatment discontinuation (efavirenz, raltegravir, or rifampicin before the end of tuberculosis treatment) counted as failures. This approach is consistent with an approach based on the time to loss of virological response (TLOVR) algorithm, recommended by the FDA. If viral load data from weeks 20 or 24 were missing and a patient's viral load at week 16 was below 50 copies per mL, we recorded treatment success.

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 mg (N=51)	Total (N=153)
Country				
Brazil	48 (94%)	49 (96%)	48 (94%)	145 (95%)
France	3 (6%)	2 (4%)	3 (6%)	8 (5%)
Men	39 (76%)	35 (69%)	38 (75%)	112 (73)
Age (years)	35 (29-45)	37 (31-44)	38 (33-43)	38 (31-44)
Ethnic origin				
Black	15 (29%)	14 (27%)	21 (41%)	50 (33%)
Mixed	15 (29%)	16 (31)	23 (45%)	54 (35)
White	21 (41%)	21 (41)	7 (14)	49 (32)
Weight (kg)	62 (52-66)	60 (51-69)	57 (50-67)	60 (51-66)
Body-mass index (kg/m ²)	21 (19-23)	21 (19-23)	20 (17-23)	21 (19-23)
History of antiretroviral treatment*	2 (4%)	2 (4%)	2 (4%)	6 (4%)
CD4 cells per μL	129 (45-308)	115 (50-213)	166 (80-367)	140 (58-302)
CD4 cell count <50 per μL	14 (27%)	12 (24%)	5 (10%)	31 (20)
HIV RNA in log ₁₀ copies per mL	5.0 (4.5-5.5)	4.9 (4.4-5.4)	4.9 (4.2-5.4)	4.9 (4.4-5.4)
HIV RNA \geq 100 000 copies per mL	26 (51%)	20 (39%)	24 (47%)	70 (46%)
Tuberculosis location				
Pulmonary only	20 (39%)	23 (45%)	23 (45%)	66 (43)
Pulmonary and extrapulmonary	26 (51)	20 (39%)	23 (45%)	69 (45%)
Extrapulmonary only	5 (10%)	8 (16%)	5 (10%)	18 (12)
Bacteriologically confirmed cases	23 (45%)	27 (53%)	25 (49%)	75 (49%)
Time between antituberculosis and antiretroviral drugs (weeks)	5.7 (4.9-7.0)	6.0 (5.0-7.1)	5.9 (5.0-6.7)	5.9 (5.0-7.0)
Hepatitis B or C co-infection	2 (4%)	8 (16%)	6 (12%)	16 (10%)

Data are n (%) or median (IQR). * Antiretroviral treatment for less than 3 months and more than 6 months before screening.

Table 1: Baseline characteristics

Secondary outcomes included virological suppression at week 48 (with the same definition as for the primary outcome), measured as the proportion of patients with plasma HIV RNA below 50 copies per mL and 400 copies per mL during follow-up; emergence of resistance-associated mutations in patients with virological failure defined as a plasma HIV RNA rebounding above 400 copies per mL; or an increase of more than 1 log₁₀ of HIV RNA at or after week 8 and confirmed 2–4 weeks later; changes from baseline in CD4 cell counts; occurrence of AIDS-defining events or death; tuberculosis treatment outcomes according to WHO definitions;¹⁸ occurrence of adverse events and serious adverse events; and paradoxical tuberculosis immune reconstitution inflammatory syndrome.²⁰ Cases of immune reconstitution inflammatory syndrome were reviewed by an independent events validation committee. Adverse events terms were adopted from the Medical Dictionary for Regulatory Activities (MedDRA US version 12.1).

Statistical analysis

We aimed to identify whether the success rate of the two raltegravir doses tested exceeded 70% at 24 weeks, which is the average response rate reported with efavirenz-based regimens in patients with HIV and tuberculosis co-infection, for further assessment in a phase III trial.^{3,21} Assuming a recorded proportion of virological success at week 24 of 85%, we calculated that, with 49 patients per group, we would be able to conclude with an α of 5% (one-sided test) and a power of 80% that the proportion of virological success at week 24 would be at least 70% if the number of failures did not exceed nine. This calculation was based on the Fleming method.²² We increased the proposed sample size to 50 patients per group to account for loss to follow-up. This study was an estimation study only, and it was not powered for formal efficacy comparison between raltegravir and efavirenz. Data were reviewed by the independent data monitoring committee every 6 months.

	Efavirenz	Raltegravir 400 mg	Raltegravir 800 mg	Total
Primary endpoint (week 24)				
Intention to treat (HIV RNA <50 copies per mL)	32/51 (63%; 49–76)	39/51 (76%; 65–88)	40/51 (78%; 67–90)	111/153 (73%; 65–80)
Per protocol (HIV RNA <50 copies per mL)	42/49 (86%; 76–96)	43/49 (88%; 79–97)	43/47 (91%; 84–99)	128/145 (88%; 83–94)
Snapshot (HIV RNA <50 copies per mL)	34/51 (67%; 54–80)	41/51 (80%; 69–91)	39/51 (76%; 65–88)	114/153 (75%; 68–81)
Secondary endpoint (week 24) Intention to treat (HIV RNA <400 copies per mL)	39/51 (76%; 65–88)	41/51 (80%; 69–91)	42/51 (82%; 72–93)	122/153 (80%; 73–86)
Secondary endpoint (week 48)				
Intention to treat (HIV RNA <50 copies per mL)	34/51 (67%; 54–80)	39/51 (76%; 65–88)	32/51 (63%; 49–76)	105/153 (69%; 61–76)
Per protocol (HIV RNA <50 copies per mL)	41/45 (91%; 83–99)	41/46 (89%; 80–98)	35/42 (83%; 72–95)	117/133 (88%; 82–93)
Snapshot (HIV RNA <50 copies per mL)	37/51 (73%; 60–85)	39/51 (76%; 65–88)	32/51 (63%; 49–76)	108/153 (71%; 63–78)
Intention to treat (HIV RNA <400 copies per mL)	37/51 (73%; 60–85)	41/51 (80%; 69–91)	33/51 (65%; 52–78)	111/153 (73%; 65–80)

Data are n/N (%; 95% CI).

Table 2: Efficacy outcomes

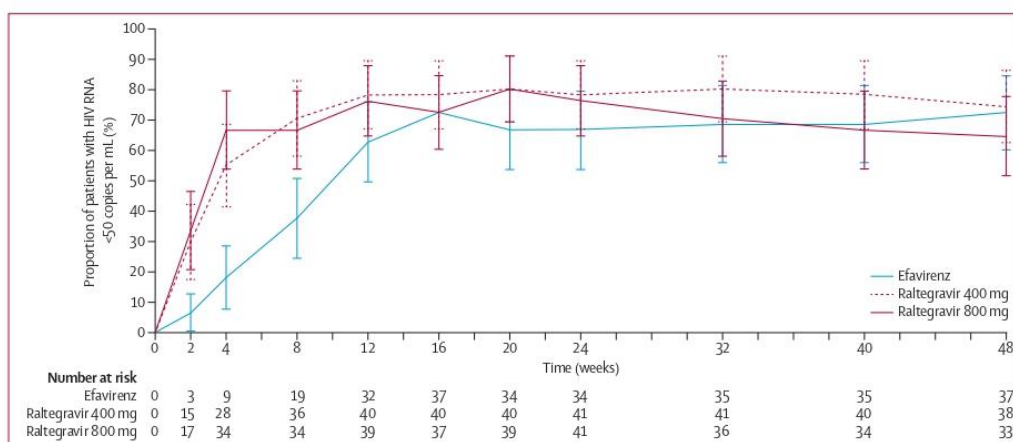


Figure 2: Virological response
Error bars are 95% CIs.

The primary efficacy analysis was a modified intention-to-treat analysis, which included all randomly allocated patients who received at least one dose of efavirenz or raltegravir. We calculated the proportion of patients with virological suppression at week 24 with 95% CIs for every group. We also did sensitivity analyses using a per-protocol analysis on available data, censoring patients who discontinued study drugs prematurely for reasons other than death or virological failure (ie, who withdrew from the study, were lost to follow-up, or had no data available), and did a snapshot analysis (the proportion of patients with HIV RNA of less than 50 copies per mL while staying on their allocated antiretroviral regimen in a time window of at most 4 weeks at weeks 24 and 48, with missing data counted as failures).

For the safety analysis, we reported the proportion of patients who had at least one grade 3–4 adverse event and one serious adverse event. We used SAS (version 9.1.3 and higher) for statistical analyses.

The study is registered in ClinicalTrials.gov, number NCT00822315.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. BG and GC had full access to all the data in the study, and JMM had the final responsibility for the decision to submit for publication.

Results

Between July 3, 2009, and June 6, 2011, we screened 179 patients, 171 in Brazil and eight in France, of whom 155 were randomly assigned treatment (we enrolled all eight patients from France): 52 to efavirenz, 51 to raltegravir 400 mg, and 52 to raltegravir 800 mg (figure 1). 153 patients (51 in each group) received at least one dose of the study drug and were included in the modified intention-to-treat analysis (figure 1). We completed follow-up of all patients on May 3, 2012.

At baseline, the number of patients with plasma HIV RNA concentrations of more than 100 000 copies per mL was slightly lower in the raltegravir 400 mg group than in the other two groups, the number of patients with CD4 cell counts below 50 cells per μ L was slightly lower in the raltegravir 800 mg group than in the other two groups, and the number of patients with hepatitis B or C co-infection was lower in the efavirenz group than in the other two groups (table 1). Baseline characteristics were otherwise much the same between treatment groups (table 1).

75 patients had bacteriologically confirmed mycobacteriosis (table 1), of whom 73 had *M tuberculosis*, one had *Mycobacterium avium*, and one had *Mycobacterium bovis*. Of the 56 cultures tested for drug susceptibility, six were streptomycin resistant, six were isoniazid resistant, and none were rifampicin resistant.

In the modified intention-to-treat analysis at week 24, our primary endpoint, we saw no between-group difference in the number of patients who achieved virological suppression (HIV RNA <50 copies per mL; table 2). The lower bound of the 95% CIs was below the predefined margin of 70% in all three groups, showing that the response rate was slightly lower than expected according to the study hypothesis. The per-protocol analysis on available data, censoring patients who discontinued efavirenz or raltegravir for reasons other than virological failure, provided similar response rates in all three groups (all lower 95% CI bounds >70%). Virological suppression rates at week 24 were slightly higher when we used a higher threshold of 400 copies per mL of HIV RNA, and we detected no between-group difference (table 2). In secondary endpoint analysis, there was again no between-group difference in viral suppression rates (HIV RNA <50 copies per mL) at week 48 (table 2). In analysis of the proportion of patients with HIV RNA concentrations lower than 50 copies per mL at each visit (figure 2), the virological response rate at week 48 was 73% (95% CI 60–85) in the efavirenz group, 75% (63–86) in the raltegravir 400 mg group, and 65% (52–78) in the raltegravir 800 mg group, with no between-group difference.

Genotypic resistance test results were available for 30 (77%) of 39 patients who had virological failure during the 48 weeks of follow-up. A similarly small proportion of patients in the two raltegravir groups developed resistance to either integrase inhibitors and NRTIs (table 3). Median

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 mg (N=51)	Total (N=153)
Virological failures*	14 (27%)	12 (24%)	13 (25%)	39 (25%)
Resistance analysis population	9 (18%)	11 (22%)	10 (20%)	30 (20%)
Developed resistance to antiretroviral regimen	6 (12%)	5 (10%)	4 (8%)	15 (10%)
Any integrase resistance mutations	0	4	4	8
E92EQ	..	1	0	1
Y143R/C	..	1	2	3
N155H	..	2	2	4
Any non-nucleoside reverse transcriptase inhibitor resistance mutations	5	5
K103N	3†	3†
V106M	1	1
Y188L	1	1
Any nucleoside reverse transcriptase inhibitor resistance mutations	6	5	3	14
M184V/I	6	5	3	14
K65R	3	3
K70E	1	1	..	2
Others (thymidine analogue mutations)	1	1	..	2

Data are n or n (%). *Defined by a confirmed plasma HIV RNA concentration higher than 400 copies per mL or a confirmed increase of more than 1 log₁₀ copies per mL at week 8 or later. †The K103N mutation was also detected in two patients in baseline samples analysed at the time of failure.

Table 3: Resistance data

increase in CD4 cell counts from baseline to week 48 was similar in all three groups (an increase of 216 [IQR 87–328] cells per μL with efavirenz, 239 [160–372] cells per μL with raltegravir 400 mg, and 212 [130–369] cells per μL with raltegravir 800 mg). Four patients in the efavirenz group and two in each of the raltegravir groups had a new AIDS-defining illness.

Overall, self-reported adherence to antiretroviral treatment was high and similar in all three groups at both week 24 (38 [95%] of 40 patients in the efavirenz group, 40 [87%] of 46 patients in the raltegravir 400 mg groups, and 32 [84%] of 38 patients in the raltegravir 800 mg group reported 100% adherence [no dose missed in the 4 days before the visit]) and week 48 (31 [94%] of 33 patients in the efavirenz group, 36 [92%] of 39 patients in the raltegravir 400 mg groups, and 27 [79%] of 34 patients in the raltegravir 800 mg group reported 100% adherence). Tuberculosis treatment success rate (cure or treatment completed) was about 90% in all three groups (table 4). Overall, the median duration of tuberculosis treatment was 6.2 months (IQR 6.0–7.2) and did not differ between the three groups.

The proportion of patients with serious adverse events was much the same in all three groups (table 5). However, the occurrence of treatment-related serious adverse events was lower in the raltegravir 400 mg group than in the efavirenz or raltegravir 800 mg groups. Also, fewer patients discontinued study drugs because of an adverse event in the raltegravir 400 mg group than in the efavirenz or the raltegravir 800 mg groups. One patient in the raltegravir 800 mg group had liver failure that was deemed to be related to the tuberculosis treatment, and underwent a liver transplant. After transplantation, raltegravir was resumed at the standard dose of 400 mg twice a day without further toxicity. The proportion of patients with grade 3 or 4 tuberculosis immune reconstitution inflammatory syndrome was low in all three groups (table 5). The proportion of patients with grade 3 or 4 laboratory abnormalities did not differ between the three groups. Seven patients died during the study (figure 1), and none of the deaths was thought to be related to the study drugs.

Discussion

We recorded no statistically significant between-group differences in patients treated with 400 mg or 800 mg of raltegravir or 600 mg of efavirenz at either week 24 or week 48. We know of no other randomised controlled trial exploring efficacy and safety of raltegravir in patients co-infected with HIV and tuberculosis (panel).

The slightly higher point estimates of efficacy at week 24 in the raltegravir groups using a threshold of 50 copies per mL were expected because the decrease in plasma HIV RNA is faster with integrase inhibitors than it is with NNRTIs. However, this rapid decrease in plasma viral load is not associated with clinical benefit,^{12,13} and with a higher

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 mg (N=51)	Total (N=153)
Treatment success	45 (88%)	46 (90%)	45 (88%)	136 (89%)
Cured	6 (13%)	8 (17%)	5 (11%)	19 (14%)
Treatment completed	39 (87%)	38 (83%)	40 (89%)	117 (86%)
Death	2 (4%)	1 (2%)	3 (6%)	6 (4%)
Default*	4 (8%)	3 (6%)	1 (2%)	8 (5%)
Treatment failure	0 (0%)	1 (2%)	1 (2%)	2 (1%)
Transferred to different centre	0 (0%)	0 (0%)	1 (2%)	1 (1%)

Data are n (%). *Patients whose tuberculosis treatment was interrupted for 2 consecutive months or more (including one patient with *Mycobacterium avium*).

Table 4: Tuberculosis treatment

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 mg (N=51)	Total (N=153)
Any adverse event	46 (90%)	46 (90%)	47 (92%)	139 (91%)
Serious adverse events	19 (37%)	17 (33%)	17 (33%)	53 (35%)
Serious adverse event related to antiretroviral treatment	10 (20%)	6 (12%)	8 (16%)	24 (16%)
Blood or lymphatic disorders	1	3	5	9
Immune system disorders	3	2	4	9
Hepatobiliary and gastrointestinal disorders	3	0	2	5
Cardiovascular disorders	1	1	1	3
Infections	1	0	0	1
Skin disorders	1	0	0	1
Any event leading to drug discontinuation	3 (6%)	0	3 (6%)	6 (4%)
Hepatotoxicity	0	0	2	2
Cutaneous rash	1	0	1	2
Gynaecomastia	1	0	0	1
Pregnancy	1	0	0	1
Grade 3–4 adverse event	19 (37%)	17 (33%)	17 (33%)	53 (35%)
Grade 3–4 immune reconstitution inflammatory syndrome	5 (10%)	2 (4%)	4 (8%)	11 (7%)
Death	2 (4%)	1 (2%)	4 (8%)	7 (5%)
Meningitis	1	0	2	3
Septic shock	1	0	1	2
Tuberculosis worsening	0	1	0	1
Unknown cause	0	0	1	1
Laboratory adverse event (any grade)	49 (96%)	49 (96%)	44 (85%)	142 (92%)
Laboratory grade 3–4	10 (20%)	13 (25%)	9 (18%)	32 (21%)
Neutrophil count <750 cells per μL	3	5	5	13
Aspartate aminotransferase >5 ULN	3	3	3	9
Alanine aminotransferase >5 ULN	3	1	1	5
Haemoglobin <7g/dL	1	2	1	4
Alkaline phosphatase >5 ULN	2	0	1	3
Platelets <50 000 cells per μL	0	2	1	3
Bilirubin >5 ULN	2	0	0	2
Creatinine >3 ULN	1	0	0	1
Glycaemia >16.5 mmol/L	0	1	0	1

Data are number of events or number of patients (%). ULN=upper limit of normal.

Table 5: Treatment-emergent adverse events, serious adverse events, and adverse events of interest

threshold at 400 copies per mL for virological suppression, we detected no between-group difference in antiretroviral activity.

At week 48, virological suppression was slightly, but not significantly higher in the standard-dose raltegravir group than in the double-dose raltegravir and the efavirenz groups. This outcome was not due to a better antiviral activity of the raltegravir 400 mg twice-daily dose, but rather to a better tolerability profile and also possibly to better adherence. Indeed, the number of patients who did not achieve a viral load of less than 50 copies per mL in the intention-to-treat analysis was similar in all three groups, suggesting that despite the interaction with rifampicin, the standard dose of raltegravir provided potent and durable antiviral activity similar to that of efavirenz. Our results are supported by data from the pharmacokinetic sub-study suggesting that the interaction between raltegravir and rifampicin is lower than expected in patients with HIV receiving

tuberculosis treatment, with no change in raltegravir's area under the concentration-time curve, and only a 31% decrease in trough concentration.²³

The antiviral activity of raltegravir and efavirenz in this trial seemed lower than in previous studies in antiretroviral-naïve patients.^{12,13} However, the rate of virological suppression in our trial was similar to that reported in patients with HIV and tuberculosis co-infection receiving efavirenz-based regimens. Indeed, in the CARINEMO-ANRS 12146 study,²¹ 199 (70%) patients achieved an HIV RNA concentration of less than 50 copies per mL at week 48. Similarly, virological response rate at week 48 in the ACTG A 5221 trial was 74% (596 of 806 patients), although a higher threshold of 400 copies per mL was used.³

CD4 cell counts increase and the occurrence of AIDS-defining events were also similar in all three groups during follow-up. Fewer patients died in the standard-dose raltegravir group than in the high-dose raltegravir group, although fewer patients in the high-dose group had low CD4 cell counts at baseline, but differences were not statistically significant.

All antiretroviral regimens were associated with very good tuberculosis treatment outcomes (although only about half were bacteriologically confirmed; table 4), and few severe or life-threatening events of immune reconstitution inflammatory syndrome occurred, probably because of the higher baseline CD4 cell counts and the longer time between initiation of tuberculosis treatment and antiretroviral treatment in this study than in others.¹⁻³

The standard dose of raltegravir in this study seemed to be well tolerated, at least as well as efavirenz and the double-dose of raltegravir. The proportion of patients with grade 3 or 4 alanine aminotransferase and aspartate aminotransferase concentration increases was much the same in all three groups. Also, no patient discontinued treatment for adverse events in the standard-dose raltegravir group and the number of serious drug-related serious adverse events were similar in all three groups. Both patients who had hepatotoxicity in this study were in the double-dose raltegravir group—one of these patients eventually had liver failure and received a liver transplant. Although this patient resumed raltegravir at the standard dose without further toxicity, the role of high-dose raltegravir in the occurrence of this serious event could be a contributing factor. Liver toxicity overall was probably underestimated in this trial because we enrolled only patients with an alanine aminotransferase concentration below 2.5 times the upper limit of normal.

In view of the potent antiviral activity of standard-dose raltegravir in combination with tenofovir and lamivudine in this trial of patients with HIV treated for tuberculosis, its favourable safety profile, its convenience and low cost compared with a double-dose regimen, this regimen is a potential first-line regimen in patients who cannot use

Panel: Research in context

Systematic review

We searched PubMed for articles published in English between Jan 1, 1970, and Feb 22, 2014, with the following search string: ("tuberculosis"[Text Word]) AND "raltegravir"[Text Word] OR ("tuberculosis"[Text Word] AND "integrase inhibitor"[Text Word]). We identified no randomised trial that compared raltegravir-based and efavirenz-based antiretroviral treatment in patients co-infected with HIV and tuberculosis treated with rifampicin. We identified only two studies reporting outcomes of patients co-infected with HIV and tuberculosis receiving a raltegravir-based regimen and rifampicin-containing tuberculosis treatment.^{15,16} In the first study,¹⁵ two patients with HIV-2 received rifampicin and raltegravir at the double dose of 800 mg twice a day and the treatment was reported to be well tolerated and effective with suppression of viral replication below 50 copies per mL in one patient. In the second study,¹⁶ eight patients received treatment, four of whom had not previously received antiretroviral treatment. All patients received raltegravir at the dose of 800 mg twice a day and treatment was reported to be well tolerated. Viral replication was suppressed in all eight patients.¹⁶ Both studies refer to our clinical trial to lend support to the recommended dose increase of raltegravir in patients co-infected with HIV and tuberculosis receiving a rifampicin-based treatment.

Interpretation

To the best of our knowledge, our trial is the first to assess the safety and efficacy of two doses of raltegravir in combination with tenofovir and lamivudine in patients co-infected with HIV and tuberculosis receiving a rifampicin-based treatment. This trial was a phase 2 study not powered for comparisons between doses, instead aiming to assess the efficacy and safety of two doses of raltegravir (standard dose of 400 mg twice daily and double dose of 800 mg twice daily) in a randomised study with a standard-of-care group receiving efavirenz-based treatment. The efficacy of all three regimens was acceptable and provided similar virological response rates to those reported in other trials in patients with both HIV and tuberculosis. Also the safety of the three regimens was good and similar, although we enrolled patients with alanine aminotransferase concentrations below 2.5 times the upper limit of normal. According to these results, the standard dose of raltegravir seems to be as good as the recommended double dose in patients with HIV and tuberculosis, with a lower cost and a lower pill burden, and might be a better alternative to efavirenz in patients unable to tolerate efavirenz or who have a contraindication to efavirenz. These findings should be substantiated in a larger phase 3 comparative study.

efavirenz. However, because of the small size of the study, these results need further assessment in a larger phase 3 trial before raltegravir at a dose of 400 mg twice a day could be regarded as a valuable alternative to efavirenz in patients with HIV and tuberculosis receiving rifampicin-based treatment.

Contributors

J-MM, NdC, GC, and BG had the idea for and designed the study. BG and J-MM led the study. GC, CG, CB, and AA designed the study and did the statistical analysis. VA, MS-O, CV, CG, GT, ST, and ER were in charge of the data management of the trial. NdC, VV, JHP, CF, GC, JVM, NB, BRS, and OP contributed to the interpretation of the results. MM and CD co-ordinated the virological analyses. GC, VA, and CF prepared the report. BG wrote the first draft and all authors reviewed and approved the final version of the paper.

Declaration of interests

J-MM has been a consultant, participated in advisory boards, has received speaker fees, and has been an investigator for clinical trials for Janssen, ViiV Healthcare, Gilead Sciences, Bristol-Myers Squibb, Abbott Laboratories, Boehringer Ingelheim, and Merck, Sharp and Dohme. He has also received research grants from Merck. CD participated in advisory boards for ViiV Healthcare, Gilead Sciences, BMS, and Merck, and has also received research grants from Gilead and MAD. CB has participated in advisory boards and has received speaker fees and travel support from Abbott, BMS, Merck, Roche, Janssen, GlaxoSmithKline, and has also received research grants from BMS, MSD, and Janssen. JVM has served on advisory boards, has received speaker fees, and has been an investigator for clinical trials for Abbott, Gilead, GSK, ViiV, Janssen, Merck, Roche, BMS, Boehringer Ingelheim, and Pfizer. GC has received consulting fees from Roche, travel grant from Lundbeck, and has had scientific responsibilities in projects receiving specific grant supports that are managed through her institution or a non-profit society from ANRS, the European Commission (framework programmes 6 and 7), UK Medical Research Council, US National Institute of Health), Foundation Plan Alzheimer, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Chiron, Fit Biotech Ltd, Gilead Sciences, GlaxoSmithKline, Jansen Cilag, Merck Sharp and Dohme-Chibret, Pfizer, Roche, Tibotec, ViiV Healthcare. CF has received a consulting fee from Merck Sharp and Dohme-Chibret and has had scientific responsibilities in projects receiving specific grant supports that are managed through her institution. All other authors declare that they have no competing interests.

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Efficacy and Safety of Efavirenz, Raltegravir, and Dolutegravir in HIV-1/TB Coinfection. A Multicenter Retrospective Cohort Study in France

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Background: There are limited data comparing the efficacy and safety of raltegravir and dolutegravir to that of efavirenz in HIV-1/tuberculosis (TB) coinfecting patients.

Methods: We conducted a 10-year retrospective study in 4 centers in France. We included all HIV-1/tuberculosis coinfecting patients starting antiretroviral therapy with a rifampicin-based regimen, with a plasma HIV RNA level (VL) > 1000 copies/mL. The primary endpoint was the proportion of patients with virological success that is, with VL <50 copies/mL at W48 using an Intention-To-Treat analysis, using last-observation-carried-forward to impute missing data. We also assessed antiretroviral therapy safety, analyzing treatment discontinuation for adverse events.

Results: Between 2010 and 2020, 117 patients were included. Thirty-nine (33.3%) were treated with raltegravir and 2 nucleoside reverse transcriptase inhibitors (NRTIs), 19 (16.2%) with dolutegravir (and 2 NRTIs) and 59 (50.4%) with efavirenz (and 2 NRTIs). At W48, the primary endpoint was achieved in 24 patients (61.5%) in the raltegravir group, in 12 (63.2%) in the dolutegravir group, and in 41 (69.5%) in the efavirenz group using an Intention-To-Treat analysis ($P = 0.68$). Emergence of drug resistance in patients with virological failure, defined as a VL >50 copies/mL, was observed in 3 patients with efavirenz and one patient with raltegravir. Rate of treatment discontinuation for drug-related adverse events was 10.3%, 10.6%, 16.9% for raltegravir, dolutegravir and efavirenz respectively ($P = 0.67$).

Conclusions: In this retrospective cohort study, raltegravir and dolutegravir yielded similar efficacy and safety results to efavirenz for the treatment of HIV-1/TB coinfecting patients.

Key Words: efavirenz, raltegravir, dolutegravir, HIV-1/TB coinfection

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INTRODUCTION

Tuberculosis (TB) is still the leading cause of death in people living with HIV, with 815,000 tuberculosis cases and 208,000 deaths worldwide reported in people living with HIV in 2019.^{1,2} Concurrent treatment of HIV and tuberculosis is essential, because it decreases mortality, the risk of relapsing tuberculosis and the transmission of tuberculosis and HIV.^{3–9}

In adults coinfecting with HIV and tuberculosis, antiretroviral therapy (ART) and TB treatment can be challenging because of increased stigma, treatment-related adverse events, drug–drug interactions, risk of immune reconstitution inflammatory syndrome and increased pill burden, that may jeopardize treatment adherence.

Drug–drug interactions between antiretrovirals and rifampicin—the cornerstone of tuberculosis treatment and a potent inducer of cytochrome P450—restrict ART options in patients coinfecting with HIV and tuberculosis. Several studies have shown that efavirenz (EFV) is less affected by the interaction with rifampicin than other antiretrovirals,^{10–14} and is therefore the treatment of choice for HIV/TB coinfection.^{15,16} However, treatment with efavirenz is not always possible because of central nervous system adverse events and transmitted drug-resistance.

Alternatives to efavirenz are therefore needed for the treatment of HIV-1-tuberculosis coinfection. Integrase inhibitors have a good safety profile and could represent an alternative to efavirenz. However, these inhibitors also have significant drug–drug interaction with rifampicin. Dolutegravir (DTG), the preferred first-line antiretroviral, is recommended at a double dose (50 mg twice daily) for patients with tuberculosis on the basis of pharmacokinetic data in healthy volunteers and on one small noncomparative trial.^{17,18} Raltegravir (RAL) seems to be an interesting option at a standard dose (400 mg twice daily) based on pharmacokinetic and safety data,^{19,20} although noninferiority of RAL

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compared with EFV was not shown in a phase 3 trial in patients with HIV-1 and TB coinfection.²¹ Nevertheless, raltegravir could be considered as an alternative, but only in selected patients.

Surprisingly, there are very few “real-life” studies on the use of integrase inhibitors in HIV-1/TB coinfecting patients,^{22–24} and particularly on the risk of emergence of integrase resistance in this context of drug–drug interactions.²⁵

The objective of our study was to evaluate, in real life, the efficacy and safety of raltegravir and dolutegravir, in comparison with efavirenz, in patients coinfecting with HIV-1/TB and starting a rifampicin-based regimen.

METHODS

Study Design and Data Collection

We conducted a retrospective multicenter observational study over 10 years (January 15, 2010 to January 15, 2020) that included individuals coinfecting with HIV-1 and TB in 4 university hospitals in Paris, France.

All 4 centers used the computerized Nadis database as electronic health record for patient follow-up and care. Demographic data, clinical outcomes, therapeutic history and laboratory tests, including CD4 and plasma HIV RNA levels (VL), were collected at each patient’s visit by the clinician. In the electronic health record, the reason for any ART change has to be reported to be able to print the patient’s prescription, so the reason for change was accurately reported. We retrospectively analyzed the charts of every patient.

Patients

Eligible patients were adult patients (>18 years old) with HIV-1 infection and treated with a rifampicin-based regimen for bacteriologically confirmed or clinically diagnosed tuberculosis, between January 2010 and January 2020, and with uncontrolled HIV-1 infection defined by VL >1000 copies/mL in the previous 12 weeks before treatment initiation.

Day 0 (D0) was defined as the first day of rifampicin and ART concurrent prescription (ie, first day of rifampicin prescription in patients who previously received a prescription of ART or first day of ART prescription for ART-naïve patients already receiving rifampicin). We included patients receiving an ART based on raltegravir and 2 nucleoside reverse transcriptase inhibitors (NRTIs), dolutegravir (and 2 NRTIs) or efavirenz (and 2 NRTIs).

We excluded patients with HIV-2 infection, rifampicin-resistant tuberculosis, latent tuberculosis, and patients who had less than 3 months of concurrent prescription of rifampicin and ART.

All patients signed an informed consent for the Nadis database, which was approved by the Paris Saint-Louis ethics committee and Commission Nationale Informatique et Libertés (CNIL) allowing the use of patients’ data for noninterventional studies without need for further consent in accordance with French regulations (CNIL, number 1171457).

Study Endpoints and Statistical Analysis

Our primary efficacy endpoint was the proportion of virologic success defined as VL <50 copies/mL using an intention-to-treat (ITT) analysis at week 48. Because of the retrospective design of this “real-life study,” we defined a window period for the primary endpoint analysis of ± 12 weeks to limit missing values. Virologic success was thus defined in our main analysis as VL <50 copies/mL at W48 and virologic failure as VL >50 copies/mL at W48, with a window period of W36 to W60. For patients who still had a missing value, we imputed missing data as last-observation-carried-forward (LOCF) in our main analysis. Sensitivity analysis was planned and performed in turn with missing data excluded, considered as virologic success and virologic failure. We compared rates of virologic success and failures between efavirenz, raltegravir, and dolutegravir-based regimens. Comparisons were also made between patients with virologic failure and virologic success, and were performed to assess whether the following baseline risks factors were associated with virologic failure: age, gender, country of birth, duration of HIV-1 infection,, antiretroviral status (naïve or experienced), baseline VL and CD4 counts, ART received at D0, and body mass index (BMI).

The secondary efficacy endpoints were proportion of virologic failure defined as VL >200 copies/mL at W48 using ITT with LOCF. We also assessed the proportion of virologic success defined as VL <50 copies/mL using the FDA snapshot algorithm at W48²⁶ and resistant mutations in case of virologic failure. In the FDA snapshot algorithm, patients were classified in the following categories: (1) virologic success defined as plasma HIV RNA level <50 copies/mL at W48 (time window W36–W60) while on their baseline ART regimen (RAL/DTG/EFV and 2 NRTIs); (2) virologic failure plasma HIV RNA level >50 copies/mL on study drugs at any visit between D0 and W48 leading to treatment discontinuation; (3) no data: missing data or lost to follow-up or discontinuation of the initial treatment for reasons other than virologic failure at a prior visit.

The primary safety endpoint was the rate of raltegravir, dolutegravir, or efavirenz discontinuation for adverse events.

We did not perform sample size and power estimation in this study and used a convenient sample of patients.

Data are presented as median with interquartile range (IQR) for continuous variables and frequencies with percentages for qualitative variables. Categorical variables were compared using Fisher exact tests whereas quantitative variables were compared using Wilcoxon signed rank tests.

All tests were two-sided at the 0.05 significance level. Analyses were performed using R statistical package (version 3.2.2: the R Foundation, Vienna, Austria).

RESULTS

Screening and Inclusion

Over the 10-year study period, we screened 587 patients with HIV/TB coinfection in our database, among which 421 TB/HIV adult patients were on concomitant rifampicin-based TB treatment and ART. We did not include

patients with missing medical files ($n = 152$). We excluded patients with a missing VL or a VL below 1000 copies/mL at baseline. We also excluded patients with less than 3 months of concurrent prescription of rifampicin and ART, and patients receiving other ART regimens. Overall, 117 TB/HIV-1 coinfecting patients who received rifampicin-based regimen and had a VL >1000 c/mL at D0 were included (see Figure, Supplemental Digital Content 1, for study flowchart, <http://links.lww.com/QAI/B909>).

Baseline Characteristics

Patients were mostly men (60.7%), with median age 40 years (IQR: 34–48), 71.9% were born in Africa and 93.2% had been infected via sexual transmission (76.1% heterosexual and 17.1% men who have sex with men). At D0, 59 patients (50.4%) received EFV + 2NRTIs, 19 (16.2%), DTG + 2NRTIs and 39 (33.3%), RAL + 2NRTIs. At D0, median VL was 6 log₁₀ (5–6), median CD4 count was 112 (60–209), and was significantly higher in the EFV-group ($P = 0.04$). In the study population, 70.1% were ART-naïve patients (62.7% in the EFV-group, 63.2% in the DTG-group and 84.6% in the RAL-group, $P = 0.04$) (Table 1).

In the RAL group, 33/39 (84.6%) patients received the standard dose (400 mg twice daily), 1 received 1200 mg daily, 5 received 1600 mg daily. In the DTG group, all patients received the recommended dose of 50 mg twice daily in combination with rifampicin. In the EFV group, 49/59 (83.1%) patients received 600 mg a day; 1 patient, 200 mg a day; and 9 patients, 800 mg daily.

Efficacy Results

At W48, using the ITT analysis with LOCF, 77 (65.8%) patients met the definition of virologic success that is, plasma HIV RNA level below 50 copies/mL (Table 2). There was no significant difference between the 3 groups with 24 patients [61.5%; confidence interval: 95% (44.7 to 76.2)] with RAL, 12 [63.2%; (38.6 to 82.7)] with DTG and 41 [69.5%; (55.9 to 80.5)] with EFV meeting the definition of virologic success ($P = 0.68$). Similarly, 29 patients [74.3%; (57.5 to 86.4)] with RAL, 12 [63.2%; (38.6 to 82.7)] with DTG, and 42 [71.2%; (57.7 to 81.9)] with EFV met the definition of virologic success using a threshold of plasma HIV RNA level < 200 copies/mL ($P = 0.69$). Similar results were observed in sensitivity analysis (see Table, Supplemental Digital Content 2, for details of sensitivity analysis, <http://links.lww.com/QAI/B910>).

Using the FDA snapshot algorithm, 38 (32.5%) patients met the definition of virologic success using a threshold of 50 copies/mL, with no difference between the groups ($P = 0.15$) (Table 2). Ten (8.5%) experienced virologic failure defined as VL >50 copies/mL at W48 or virologic failure before W48 leading to treatment discontinuation. Five (4.3%) were lost to follow-up, one patient died from a non-ART-related cause, and 14 (8.8%) could not be classified as success or failure, because of lack of available VL at W48. Forty-nine patients (41.9%) discontinued initial ART-regimen because of an adverse event or other reason: 22 (56.4%) in the RAL group, 10 (52.6%) in the DTG, and 17 (28.8%) in the EFV group

($P = 0.01$). There was a significant difference in treatment discontinuation for therapeutic simplification, with 12 patients (30.8%), 6 (31.6%), and 1 (1.7%) in the RAL, DTG, and EFV group respectively ($P < 0.001$). All those 18 patients in the RAL and DTG groups had their treatment simplified for a one-pill regimen at the end of TB treatment, underlining the potential difficulty in adhering to twice-daily ISNTI dosing.

Virologic Failure and Resistance

Ten (8.5%) patients experienced virologic failure while on their initial antiretroviral regimen: 5 had an HIV RNA > 50 copies before W48 leading to treatment discontinuation and 5 at W48.

Results of genotypic resistance at time of virologic failure were available for 8 patients and not performed or not available for the 2 other patients. Among the 8 patients with available genotype, 3 had NRTI, 4 NNRTI, and one INSTI RAMs. Of these 8 patients, comparison with genotype before the virologic failure was possible in 6. Emergence of drug resistance in patients with virologic failure was observed in 3 patients with EFV (K103H, E138K, Y181C respectively), one with RAL, and none with DTG. Details are described in Table, Supplemental Digital Content 3, <http://links.lww.com/QAI/B911>.

Risk Factors for Virological Failure

Comparisons between patients with virologic failure and virologic success were performed to assess whether the following baseline risk factors were associated with virologic failure: age, gender, country of birth, duration of HIV-1 infection, antiretroviral status, baseline VL and CD4 counts, ART received at D0, and BMI. There was no significant difference between the 3 groups. Details are described in Table, Supplemental Digital Content 4, <http://links.lww.com/QAI/B912>.

Safety Results

Among the 49 (41.9%) treatment discontinuations, 16 (13.7%) were related to adverse events. Rate of treatment discontinuation for drug-related adverse events was 10.3%, 10.6%, 16.9% with raltegravir, dolutegravir, and efavirenz respectively ($P = 0.67$) (Table 2). Six patients presented vivid dreams (all in the EFV group); 2, transaminase elevation; 2, skin rashes; 1, creatinine elevation; and 5, gastrointestinal symptoms.

DISCUSSION AND CONCLUSIONS

In this retrospective cohort study, raltegravir and dolutegravir yielded similar efficacy compared with efavirenz for the treatment of patients coinfecting with HIV-1 and TB.

The proportion of virologic success using an ITT analysis was similar to that reported in the Reflate TB 2 clinical trial, where success rates of 61%–66% have been reported.²¹ Using the FDA snapshot algorithm, the proportion of virologic success was lower (32.5%); these differences can

TABLE 1. Baseline Characteristics of the Population

Characteristics	EFV + 2NRTIs 59 (50.4)	DTG + 2NRTIs 19 (16.2)	RAL + 2NRTIs 39 (33.3)	Total 117 (100.0)	P
Sex, no. of patients (%)					0.66
Male	37 (62.7)	10 (52.6)	24 (61.5)	71 (60.7)	
Female	19 (32.2)	8 (42.1)	15 (38.5)	42 (35.9)	
Transgender	3 (5.1)	1 (5.3)	0 (0.0)	4 (3.4)	
Country of birth, no. of patients (%)					0.52
Sub-Saharan Africa	40 (71.4)	12 (63.2)	30 (76.9)	82 (71.9)	
France	6 (10.7)	3 (15.8)	3 (7.7)	12 (10.5)	
South America	4 (7.1)	0 (0.0)	1 (2.6)	5 (4.4)	
Asia	2 (3.6)	3 (15.8)	1 (2.6)	6 (5.3)	
Others	4 (7.1)	1 (5.3)	4 (10.3)	9 (7.9)	
NA	3	0	0	3	
Transmission, no. of patients (%)					0.96
Heterosexual	44 (74.6)	14 (73.7)	31 (79.5)	89 (76.1)	
Homo and/or bisexual	10 (16.9)	4 (21.1)	6 (15.4)	20 (17.1)	
Others or unknown	5 (8.5)	1 (5.3)	2 (5.1)	8 (6.8)	
Age in yr, median (IQR)	40 (34–48)	44 (34–49)	39 (33–47)	40 (34–48)	0.69
Time since HIV diagnosis in mo, median (IQR)	2 (1–27)	2 (1–4)	1 (1–3)	2 (1–5)	0.16
Antiretroviral status					0.04
Naive	37 (62.7)	12 (63.2)	33 (84.6)	82 (70.1)	
Treatment-experienced	22 (37.3)	7 (36.8)	6 (15.4)	35 (29.9)	
NRTIs used					0.09
TDF/FTC or TDF/3TC	56 (94.9)	15 (78.9)	36 (92.3)	107 (91.5)	
ABC/3TC	3 (5.1)	4 (21.1)	3 (7.7)	10 (8.5)	
CD4 cells in/mm ³ , median (IQR)	122 (59–193)	108 (80–206)	102 (53–287)	112 (60–209)	0.04
CD4 cells in/mm ³					0.37
<50	14 (24.1)	2 (11.8)	8 (24.2)	24 (22.2)	
50–200	32 (55.2)	10 (58.8)	14 (42.4)	56 (51.9)	
200:350	7 (12.1)	2 (11.8)	6 (18.2)	15 (13.9)	
350:500	5 (8.6)	1 (5.9)	4 (12.1)	10 (9.3)	
≥500	0 (0.0)	2 (11.8)	1 (3.0)	3 (2.8)	
VL in log ₁₀ c/mL, median (IQR)	6 (5–6)	6 (5–6)	5 (5–6)	6 (5–6)	0.50
VL in log ₁₀ c/mL					0.65
≤5	16 (27.1)	4 (21.1)	13 (33.3)	33 (28.2)	
>5	43 (72.9)	15 (78.9)	26 (66.7)	84 (71.8)	
Concomitant HCV infection*	3 (5.4)	2 (11.1)	0 (0.0)	5 (4.5)	0.14
Concomitant HBV infection†	11 (19.3)	1 (5.6)	3 (7.9)	15 (13.3)	0.23
BMI, kg/m ²	22 (20–24)	22 (20–24)	21 (19–24)	22 (20–24)	0.81

*Positive HCV serology.

†Positive HBsAg.

3TC, lamivudine; ABC, abacavir; FTC, Emtricitabine; TDF, Tenofovir; VL, plasma HIV RNA level.

be explained in part by a higher rate of patients discontinuing the study drugs because of drug-related adverse events and therapeutic simplification, lost to follow-up or other reasons in our study compared with prior randomized trials (Table 2).

In our patients, the safety and tolerability of RAL, DTG, and EFV was good. The rate of study drug discontinuation for adverse events, although higher than in prior randomized studies, remained relatively low (13.7%) and was because of mild adverse events such as vivid dreams, mostly in the EFV group.

The strength of our study is to have included patients with different treatment history and to compare, in a high-

income country, the efficacy and safety of raltegravir and dolutegravir, in comparison with efavirenz, in patients coinfecting with HIV-1/TB.

As mentioned previously, our analysis has the inherent limitations of retrospective, nonrandomized studies. We also used an LOCF technique to impute missing data in the ITT analysis, which may introduce bias, but sensitivity analyses (assigning patients with missing data to the success or failure group) did not change the interpretation of our results. In addition, because of the retrospective design of our study, we could not assess a number of potential risk factors for virologic failure such as substance and alcohol abuse,

TABLE 2. Virological Success at W48

	EFV + 2NRTIs	DTG + 2NRTIs	RAL + 2NRTIs	Total	P
ITT analysis LOCF—no. of patients (%)	59	19	39	117	
Virological success: VL < 50 c/mL	41 (69.5)	12 (63.2)	24 (61.5)	77 (65.8)	0.69
VL > 50 c/mL	18 (30.5)	7 (36.8)	15 (38.5)	40 (34.2)	
VL > 200 c/mL	17 (28.8)	7 (36.8)	10 (25.6)	34 (29.1)	0.68
FDA snapshot algorithm—no. of patients (%)	59	19	39	117	
Virologic success: VL < 50 c/mL	24 (40.7)	4 (21.1)	10 (25.6)	38 (32.5)	0.16
Virologic failure: VL > 50 c/mL at W48 or virologic failure before W48 leading to treatment discontinuation	5 (8.5)	2 (10.5)	3 (7.7)	10 (8.5)	0.99
No data	30 (50.8)	13 (68.4)	26 (66.7)	69 (59.0)	0.18
Treatment discontinuation	17 (28.8)	10 (52.6)	22 (56.4)	49 (41.9)	0.01
Adverse events	10 (16.9)	2 (10.5)	4 (10.3)	16 (13.6)	0.67
Therapeutic simplification	1 (1.7)	6 (31.6)	12 (30.8)	19 (16.2)	<0.001
Pregnancies	1 (1.7)	0 (0.0)	1 (2.6)	2 (1.7)	0.99
Nonadherence	0 (0.0)	1 (5.3)	3 (7.7)	4 (3.4)	0.06
Other reasons	5 (8.5)	1 (5.3)	2 (5.1)	8 (6.8)	0.88
Death	0 (0.0)	1 (5.3)	0 (0.0)	1 (0.9)	0.16
Lost-to-follow-up	5 (8.5)	0 (0.0)	0 (0.0)	5 (4.3)	0.11
Missing data at W48	8 (13.6)	2 (10.5)	4 (10.3)	14 (12.0)	0.92

depressive disorder, mental illness, poverty/homelessness, and previous virologic failure with ART. Finally, the small number of patients included in our study lacked power to identify risk factors for virologic failure.

In conclusion, our results are consistent with current guidelines recommending efavirenz based regimen for the treatment of HIV-1/TB coinfection, and the use of integrase inhibitors as alternatives.

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Appendix 3: Tuberculosis incidence and list of high burden countries in 2020 [1]

Figure S1 : estimated TB incidence rates, 2020 [1]

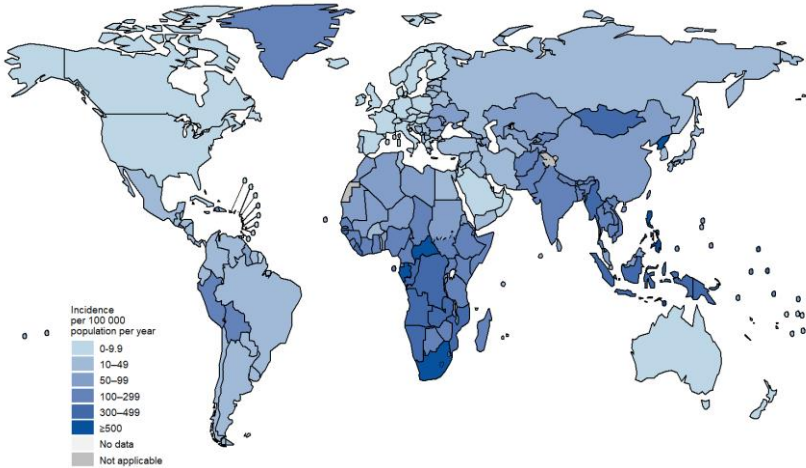


Figure S2: Estimated HIV prevalence in new and relapse TB cases, 2020 [1]

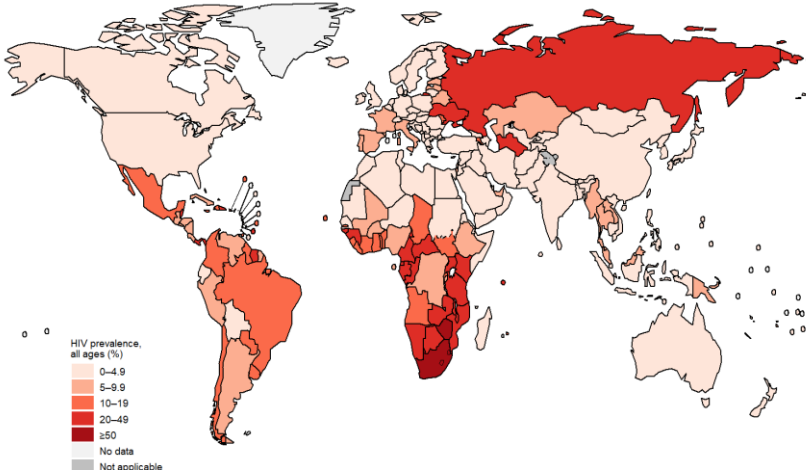
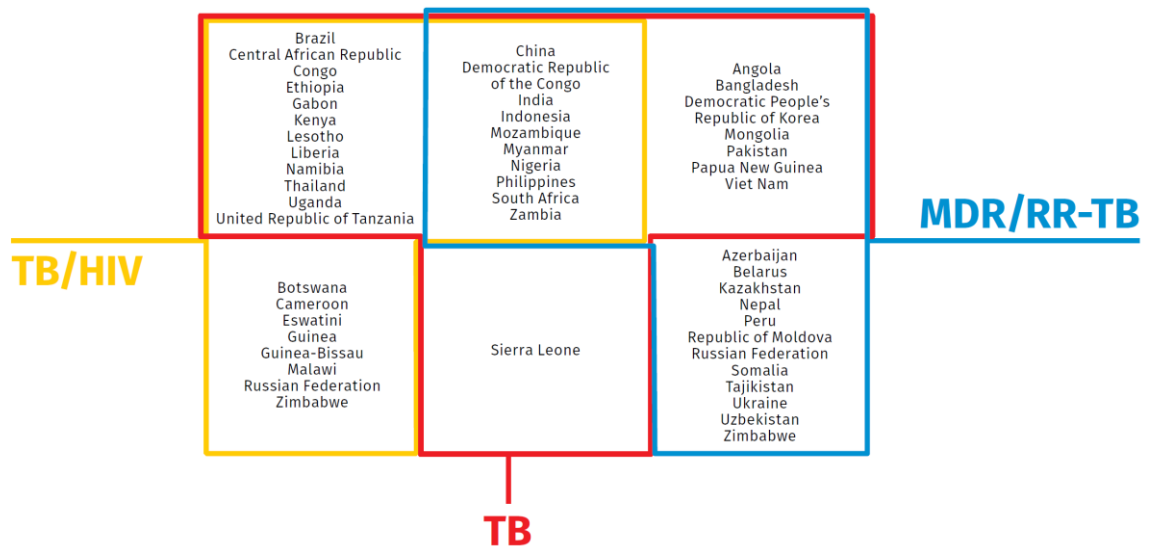
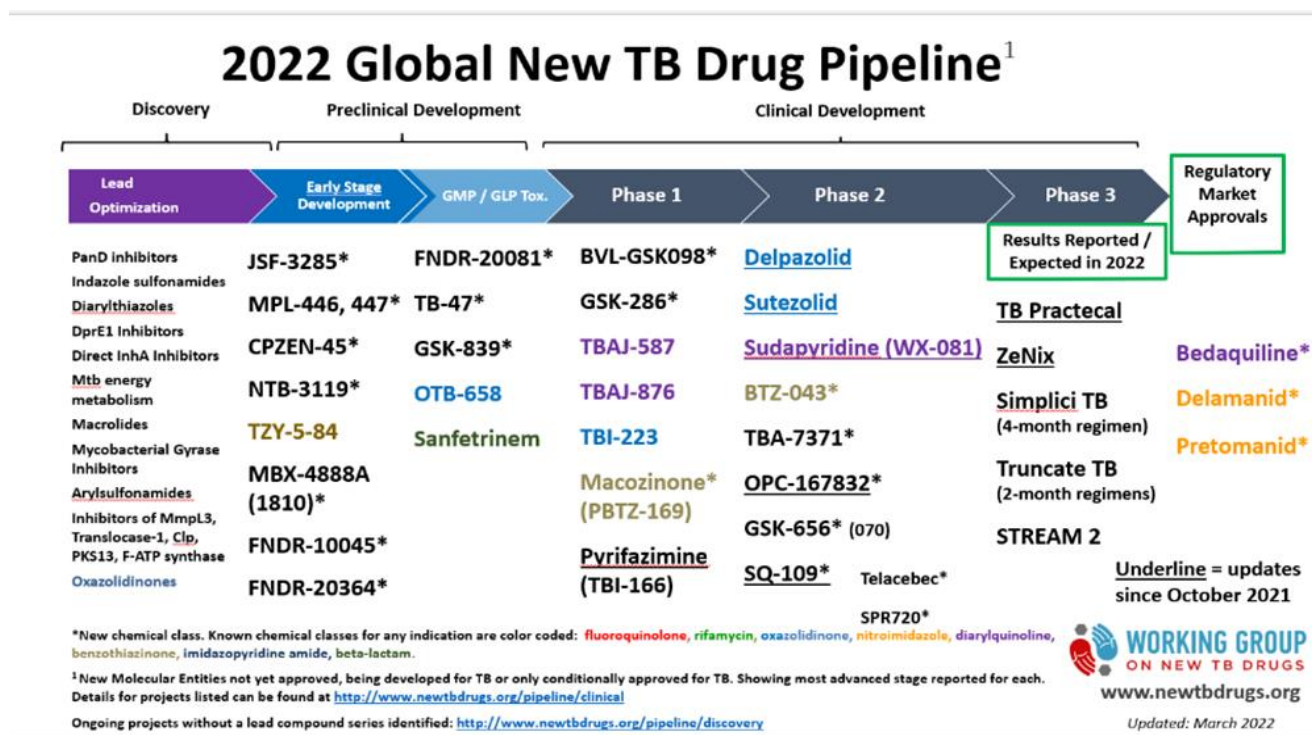


Figure S3 : The three global lists of high-burden countries for TB, HIV-associated TB and MDR/RR-TB to be used by WHO in the period 2021–2025, and their areas of overlap [1]

















Appendix 4: list of drugs under development for the treatment of tuberculosis

Figure S1: TB drug pipeline in 2022






















Appendix 5: Antiretroviral therapy combinations approved in the United Kingdom 2019/2020

(Leaflet available at: <https://i-base.info/guides/starting/arvs>)

Antiretroviral drugs 2019/20		www.i-base.info	
Drug names		Recommended adult dose *	Total daily pills
Fixed dose combinations			
Atripla (efavirenz + emtricitabine + tenofovir DF)		One tablet, once-daily. Take at night and not with a high fat meal. See info on separate drugs.	1
Biktarvy (bictegravir + TAF + emtricitabine)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Eviplera (rilpivirine + emtricitabine + tenofovir DF)		One tablet, once-daily, with food (400 kcal). See separate drug info.	1
Odefsey (rilpivirine + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Triumeq (dolutegravir + abacavir + lamivudine)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Genvoya (elvitegravir + cobicistat + emtricitabine + TAF)		One tablet, once-daily. Take with food. See info on separate drugs.	1
Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir DF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Symtuza (darunavir + cobicistat + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Delstrigo (doravirine + lamivudine + tenofovir DF)		One tablet, once-daily, with or without food. See info on each drug.	1
Dovalo (dolutegravir + lamivudine)		One tablet, once-daily, with or without food. See info on each drug.	1
Juluca (dolutegravir + rilpivirine)		One tablet, once-daily, take with food. See info on separate drugs.	1
Dual nukes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)			
tenofovir DF 300 mg + emtricitabine 200 mg (Truvada [pictured] or generic) **		One tablet, once-daily.	1
TAF (10 mg white or 25 mg blue) + emtricitabine (200 mg), Descovy		One tablet, once-daily.	1
abacavir 600 mg + lamivudine 300 mg (Kivexa or generic) **		One tablet, once-daily.	1
Single nukes (NRTIs)			
Single nukes are only used in a few situations. See back page of this leaflet for single versions of tenofovir DF, emtricitabine, abacavir and lamivudine.			

* Different doses or formulations might be used - always check doses with your pharmacist.
 ** Generic versions might be a different colour and shape. \$ EU approval pending.

Phoneline 0808 800 6013		Monday–Wednesday 12 noon–4pm	
NNRTIs: non-nucleoside reverse transcriptase inhibitors (non-nukes)			
efavirenz 600 mg or 200 mg (Sustiva, [pictured] or generic) **		1 x 600 tablet (or 3 x 200 caps) once-daily, at night, not with high fat meal.	1 tablet (or 3 capsules)
nevirapine PR 400 mg (Viramune [pictured] or generic) **		1 x 400 mg once a day. Take with or without food.	1 x 400 mg
etravirine (100 mg or 200 mg) (Intelect)		2 x 100 mg OR 1 x 200 mg, twice daily, take with food. Dispersible in water.	2 or 4
rilpivirine (Edurant)		1 x 25 mg tablet, once-daily, take with main meal (500 kcal).	1
doravirine (Pifeltro)		1 x 100 mg tablet, once-daily, take with or without food.	1
INIs or INSTIs: integrase inhibitors			
raltegravir 400 mg (pink) & 600 mg (yellow) (Isentress)		1 x 400 mg, twice-daily OR 2 x 600 mg tablet, once-daily. Take with or without food.	2
dolutegravir (Tivicay) *		1 x 50 mg tablet, once-daily (or 1 x 50 mg twice-daily). With food if twice-daily but with or without otherwise.	1 or 2
elvitegravir and bictegravir are only in combination pills – see Stribild, Genvoya and Biktarvy.			
CCRS inhibitors (entry inhibitor)			
maraviroc * (Celsentri)		150 mg or 300 mg or 600 mg, as directed, depending on other ARVs in the combination.	1 or 2 or 4
b/PI: boosted protease inhibitors			
atazanavir * (Reyataz)		1 x 300 mg cap + booster, once-daily. Take with food. 150 mg and 200 mg capsules also available.	1 (+ 1 booster)
darunavir 600 mg (orange) & 800 mg (red), (Prezista) *		1 x 800 mg + booster once-daily (OR 1 x 600 mg + 100 mg booster twice-daily with resistance). Take with food.	1 or 2 (+ 1 or 2 boosters)
atazanavir/cobicistat (Evotaz)		1 tablet, once-daily. Take with food.	1
darunavir/cobicistat (Rezolsta)		1 tablet, once-daily. Take with food.	1
PK (pharmacokinetic) boosters			
cobicistat (c) (Tybost)		150 mg tablet, once daily. Used to boost atazanavir, darunavir and elvitegravir.	depends on boosted drug
ritonavir (r) * (Norvir)		100 mg tablets used at different doses to boost other PIs.	depends on PI

Drug names		Recommended adult dose *	Total daily pills
Single nukes (NRTIs)			
lamivudine (3TC) (EpiVir [pictured] or generic)		1 x 300 mg (shown) or 2 x 150 mg, (taken as a once-daily or twice-daily dose).	1 if 300 mg 2 if 150 mg
abacavir ** (Ziagen [pictured] or generic)		2 x 300 mg tablets (taken as a once-daily or twice-daily dose).	2
emtricitabine (FTC) (Emtriva)		1 x 200 mg capsule, once-daily.	1
tenofovir DF * ** (Viread [pictured] or generic)		1 x 300 mg tablet, once-daily.	1
bNAbs (broadly neutralising monoclonal antibody) - an immune-based treatment			
ibalizumab § (Trogarzo)		150 mg/mL given as single IV infusion every two weeks.	none

Notes to drug chart

Some drugs are not recommended for first-line therapy. Paediatric formulations can sometimes be used in adults if larger pills are difficult to swallow. Sometimes granules or liquids are available. Pictures approximate to actual size.

Drugs that are used less frequently

Many older HIV drugs are now rarely used. Information about these older drugs is available online. <http://i-base.info/guides/category/arvs>

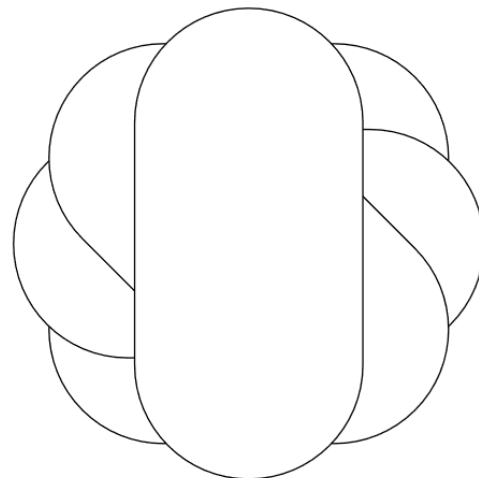
Please call i-Base if you would like information about other drugs printed and posted to you. These include zidovudine (AZT), stavudine (d4T), zidovudine with lamivudine, Trizivir, lopinavir, fosamprenavir, tipranavir and efavirtide (T-20).

Future drugs and combinations

If new drugs are approved during 2020, details will be posted online. <http://i-base.info/guides/category/arvs>
 After drugs are approved in Europe it usually takes the NHS from 6 to 12 months to decide on UK access.

ARV chart 2019/20

October 2019



www.i-base.info



www.hivpa.org

A supplement to the i-Base Introduction to ART

Appendix 6: Supplementary material to the publication “Standard Dose Raltegravir or Efavirenz Based Antiretroviral Treatment for HIV-1-Infected Adults with Tuberculosis: A Phase 3, Randomized, Open-Label, Non-Inferiority Trial”.

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Supplementary methods

Full eligibility criteria

Inclusion criteria

- Signed informed consent form
- Aged 18 years or more
- Confirmed HIV-1 infection as documented at any time prior to trial entry per national HIV testing procedures
- ART naïve
- For women of childbearing potential i.e. women of childbearing age who are not menopausal, or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) or not refraining from sexual activity: negative urinary test for pregnancy and acceptance to use contraceptive methods
- Confirmed or probable active TB disease of any location, except neurological (meningitis or encephalitis), according to the following criteria based on WHO updated definitions (see Appendix 4)
 - Bacteriologically confirmed pulmonary TB (PTB) or extrapulmonary TB (EPTB), e.g. TB with a biological specimen positive by smear microscopy, culture or nucleic acid amplification test (such as Xpert MTB/RIF)
 - Clinically diagnosed PTB or EPTB with:
 - Typical histological evidence of TB (caseous or granulomatous) on biopsy specimen or positive urinary LAM test
 - OR
 - A significant improvement on TB treatment
- Ongoing standard rifampin-containing TB treatment for ≤ 8 weeks at inclusion

Is considered a standard TB treatment a daily regimen containing rifampin, isoniazid, ethambutol and pyrazinamide for 2 months (intensive phase) followed by 4 months of daily rifampin and isoniazid (continuation phase). TB treatments with prolonged continuation phase for specific forms of EPTB, or addition of ethambutol in the continuation phase, as proposed in populations of known or suspected high levels of isoniazid resistance, are also considered standard.
- For patients in France, affiliation to a Social Security program, CMU (Universal Health Cover) or AME (State Medical Aid)²

² Country specific for France (not to be translated): given the large proportion of beneficiaries of AME among the population usually affected by tuberculosis and HIV co-infection, it appears essential to include patients with AME to enable enrolment in France. In routine care, AME beneficiaries access to identical care and treatment than patients with social security or CMU.

There are no inclusion criteria based on CD4 T-cell count.

Non-inclusion criteria

- HIV-2 co-infection
- Impaired hepatic function (icterus or ALT (SGPT) > 5ULN)
- Hemoglobin < 6.5 g/dL
- Creatinine clearance <60mL/min (assessed by the Cockcroft and Gault formula; see Appendix 5)
- Mycobacterium tuberculosis strain resistant to rifampin (current or past history).

Xpert MTB/RIF, line probe assays or culture with drug susceptibility testing (DST) can be used to assess resistance to rifampin. Probable cases of TB without drug-resistance data can be included.

- Neurological TB (meningitis or encephalitis)
- Severe associated diseases requiring specific treatment (including all specific AIDS defining illnesses other than TB, and any severe sepsis)
- Any condition which might, in the investigator's opinion, compromise the safety of treatment and/or patient's adherence to trial procedures including very severe TB-related clinical condition
- Concomitant treatments including phenytoin or phenobarbital (compounds interacting with UGT1A1)
- For HCV co-infected patients, need to start specific treatment for hepatitis during the trial duration
- For women of childbearing potential:
 - Pregnancy or breastfeeding
 - Refusal to use a contraceptive method
 - Any history of ARV intake for prevention of mother to child transmission of HIV (pMTCT)
- Subjects participating in another clinical trial evaluating therapies and including an exclusion period that is still in force during the screening phase
- Person under guardianship, or deprived of freedom by a judicial or administrative decision

Detailed follow-up

We performed clinical examination and laboratory analyses at screening, and inclusion (baseline) visits, and follow-up visits at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48.

Patients were diagnosed with confirmed or probable tuberculosis according to WHO guidelines(14), and started anti-tuberculosis treatment at clinics before referral to the trial site (14) (see supplementary appendix). Smear microscopy, Xpert® MTB/RIF (Cepheid, Sunnyvale, Ca. USA), and mycobacterial cultures results on expectorated sputum and relevant extrapulmonary samples were either collected if performed at diagnosis or

obtained on newly collected at the time of tuberculosis diagnosis were collected, or samples performed at the screening visit, if not available. Chest radiographs were also performed at the screening visit, unless performed recently for tuberculosis diagnosis.

For tuberculosis follow-up, sputum smear microscopy and culture, and chest radiographs were repeated performed, per National Guidelines, and at least at week 8. Patients were tested for hepatitis B (detection of hepatitis B surface antigen), and hepatitis C (detection of hepatitis C virus specific antibodies), at the screening visit.

We measured plasma HIV-1 RNA levels at visits W0, W4, W12, W24, W32, W40, and W48 visits using the COBAS Taqman HIV-1 test assay v2.0 (Roche Diagnostics, Meylan, France) in France, Côte d'Ivoire, Mozambique, and Vietnam, and the Abbot Real time in Brazil. We assessed presence of genotypic resistance mutations to NRTIs, NNRTIs, and integrase inhibitors in patients with virologic failure, by sequencing the reverse transcriptase and integrase genes, and reporting mutations using the consensus technique of the ANRS AC11 Resistance Group (www.hivfrenchresistance.org), both at the time of confirmed virologic failure and at baseline, using stored plasma specimens available on site.

All virology laboratories followed external quality control programs consisting in monthly HIV-1- RNA measurements on aliquots prepared by the trial central virology laboratory (Saint Louis Hospital, Paris, France) and yearly genotypic resistance tests quality controls organized by the "Centre National de Référence du VIH" in association with ANRS.

We measured CD4 cell counts at baseline, W4, W12, W24, W48 visits by flow cytometry, and . We measured full blood cell counts, creatinine, and alanine aminotransferase (ALT) levels at W4, W8, W12, W24, W48 (and W2 for ALT). We, and performed urinary pregnancy tests at screening visits, W0, W4 visits and every follow-up visit thereafter for women of childbearing potential.

We monitored adherence to antiretroviral drugs at every follow-up visit using pill count and interviewing patients about missed doses in the past 4 days and the month prior to the visit.

Pill count ratio

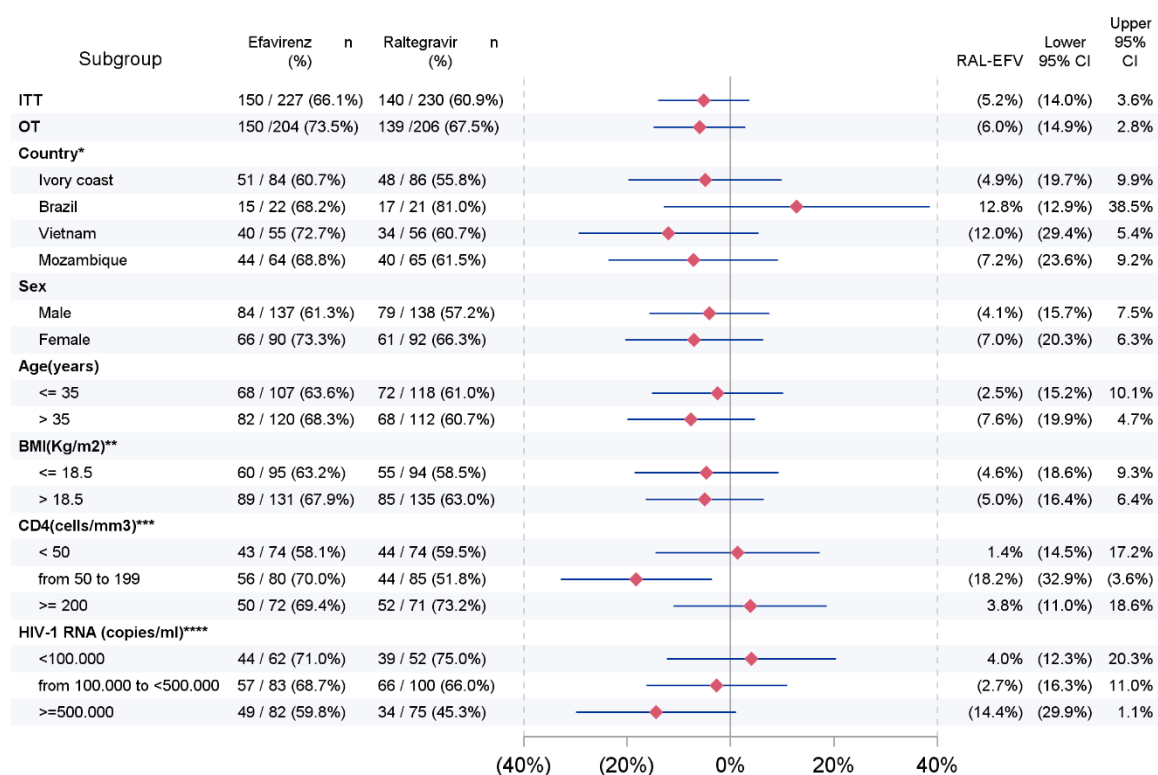
Pill count adherence ratio = (Total number of pills delivered - total number of pills returned)/total number of pills prescribed

For efavirenz the total number of pills prescribed is calculated as follows: (Last date in the trial – date of randomization) – duration of allocated treatment interruption*.

For Raltegravir, the total number of pills prescribed is calculated as follows: 2x [(Last date in the trial – date of randomization) – duration of allocated treatment interruption*].

*Treatment interruption is the addition of all reasons of temporary or permanent allocated treatment interruption

Figure S1. Subgroup analysis for the primary endpoint (ITT population)



* excluding patients from France (N=4; 0/2 and 1/2 in virologic success in the efavirenz and raltegravir arm respectively)

** excluding one patient in each arm with missing BMI

*** excluding one patient in efavirenz arm with missing CD4

****excluding 3 patients with baseline HIV-1 RNA missing in raltegravir arm

Numbers in bracket are negative.

Table S1. Genotypic resistance tests in patients experiencing virological failure in the ANRS Reflate TB 2 trial

	Efavirenz arm (N=33)		Raltegravir arm (N=42)	
	At failure	At W0	At failure	At W0
Amplified for genotype on reverse transcriptase.	32	33	41	39
NRTI mutations*	17 (53)	0 (-)	25 (61)	2 (5)
M41L	0	0	1	1
K65R	9	0	2	0
D67N	1	0	1	0
K70R	1	0	1	0
L74V/I	3	0	0	1
M184V	13	0	22	0
T215A/C	0	0	2	2
NRTI resistance*	17 (53)	0 (-)	25 (61)	2 (5)
Tenofovir	11	0	2	0
Lamivudine	17	0	22	0
Zidovudine	0	0	2	2
Abacavir	11	0	2	1
Tenofovir-Lamivudine	11	0	3	0
NNRTI mutations*	22 (69)	5 (15)	4 (10)	2 (5)
K101E	4	1	0	0
K103N	17	5	3	1
Y181C	3	0	0	0
Y188C	2	0	0	0
G190A	5	0	1	1
NNRTI resistance*	22 (69)	5 (15)	4 (10)	2 (5)
Efavirenz	22	5	4	2
Tenofovir-Lamivudine-Efavirenz	10	0	0	0

	Efavirenz arm (N=33)		Raltegravir arm (N=42)	
	At failure	At W0	At failure	At W0
Amplified for genotype (integrase)	26	33	32	39
Integrase mutations†	2 (8)	2 (6)	12 (38)	0 (-)
E92Q	0	0	1	0
G140C/S	0	0	2	0
Y143A/C/G/H/R/S	0	0	4	0
Q148K	0	0	2	0
N155H	0	0	6	0
E157Q‡	2	2	3	0
Integrase resistance†	2 (8)	2 (6)	12 (38)	0 (-)
Raltegravir	2	2	12	0
Dolutegravir§	0	0	3	0
Tenofovir-Lamivudine-Raltegravir	1	0	2	0

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI non-nucleoside reverse transcriptase inhibitor

*Proportion among patients with genotypic resistance tests available for reverse transcriptase

†Proportion among patients with genotypic resistance tests available for integrase

‡The mutation E157Q confers low level resistance to dolutegravir

§resistance profiles to dolutegravir are: E92Q+N155H (n=1); G140A/X+Q148K/X (n=2);

Table S2 Tuberculosis treatment outcomes in the ANRS Replate TB 2 trial

	Efavirenz arm	Raltegravir arm
	(N=227)	(N=230)
Treatment success – no. (%)	203 (89.4)	209 (90.9)
Cured	123 (54.2)	111 (48.3)
Treatment completed	80 (35.2)	98 (42.6)
Death* – no. (%)	10 (4.4)	12 (5.2)
Treatment failure† – no. (%)	5 (2.2)	1 (0.4)
Lost to follow-up – no. (%)	5 (2.2)	5 (2.2)
Transferred out – no. (%)	3 (1.3)	2 (0.9)
TB treatment ongoing at the end of the trial – no. (%)	0	1 (0.4)
Missing outcome – no. (%)	1 (0.4)	0

*4 additional patients died between the end of TB treatment and W48 in the efavirenz arm

†Patients whose tuberculosis treatment was interrupted for 2 consecutive months or more or with smear or culture positive at 5 months or later).

TB : tuberculosis

Table S3. Causes of death

No.	Trial arm	Cause of death
1	Raltegravir	Neck injury
2	Raltegravir	Brain abscess
3	Raltegravir	Drug reaction with eosinophilia and systemic symptoms
4	Raltegravir	Unknown cause of death
5	Efavirenz	Sepsis
6	Efavirenz	Respiratory distress
7	Raltegravir	Unknown cause of death
8	Efavirenz	Sepsis
9	Raltegravir	Unknown cause of death
10	Raltegravir	Immune reconstitution inflammatory syndrome associated tuberculosis
11	Efavirenz	Cerebral toxoplasmosis
12	Raltegravir	Sepsis
13	Efavirenz	Acute renal failure
14	Efavirenz	Kaposi's sarcoma
15	Raltegravir	Atypical mycobacteria
16	Raltegravir	Meningoencephalitis
17	Efavirenz	Acute respiratory failure
18	Efavirenz	Unknown cause of death
19	Efavirenz	Atypical mycobacteria
20	Efavirenz	Hepatocellular carcinoma
21	Efavirenz	Immune reconstitution inflammatory syndrome associated tuberculosis
22	Efavirenz	Unknown cause of death
23	Raltegravir	Meningitis cryptococcal
24	Efavirenz	HIV wasting syndrome
25	Efavirenz	Disseminated tuberculosis
26	Raltegravir	Unknown cause of death

Appendix 7: Editorial comment: « Raltegravir in patients with tuberculosis »

This editorial by Anton Pozniak and Graeme Meintjes was published in the *Lancet Infectious Diseases* on June 2021 together with our paper presenting the results of the ANRS 12300 Reflate TB2 trial.

Comment

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Raltegravir in patients with tuberculosis



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See [Articles](#) page 813

Treatment of patients with tuberculosis and HIV infection is complex, with pill burden and treatment adherence presenting major challenges. Rifampicin is a potent inducer of hepatic cytochrome P450 and uridine diphosphate glucuronosyl transferase 1A1 enzymes and the drug efflux pump P-glycoprotein, with potential for major drug–drug interactions with many antiviral drugs. Before publication of the ANRS 12300 Reflate TB 2 study by Nathalie De Castro and colleagues¹ in *The Lancet Infectious Diseases*, the only other randomised phase 3 controlled trials of rifampicin and antiretroviral regimens included the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz.^{2,3} Benefits of efavirenz include that no dose adjustments are required with rifampicin and it is available in single pill once a day combinations. However, in most guidelines efavirenz is no longer the recommended first-line HIV treatment due to its neuropsychiatric side-effects, increased risk of suicide, and concerns regarding increasing prevalence of transmitted primary NNRTI resistance, as observed in antiretroviral therapy (ART) programmes in low-income and middle-income countries (LMICs).⁴

The open-label, randomised, phase 3 ANRS 12300 Reflate TB 2 study assessed the non-inferiority of integrase strand-transfer inhibitor (INSTI) raltegravir 400 mg twice daily to efavirenz in ART-naïve patients within 2–8 weeks of commencing treatment for tuberculosis.¹ On the basis of the tolerability and efficacy of raltegravir 400 mg twice daily with tuberculosis treatment in the previous phase 2 Reflate TB study⁵ and on data from the associated pharmacokinetic substudy,⁶ it was anticipated that the raltegravir

group would meet the prespecified non-inferiority margin of –12% with respect to the primary endpoint of virological suppression (HIV RNA <50 copies per mL) at week 48. In the intention-to-treat population, 140 (61%) of 230 participants in the raltegravir group and 150 (66%) of 227 patients in the efavirenz achieved virological suppression (between-group difference –5.2% [95% CI –14.0 to 3.6]). Thus, since the lower bound of the 95% CI was –14%, raltegravir did not show non-inferiority compared with efavirenz.

Although the proportion of participants who had achieved virological suppression at week 48 was lower than that used to derive the sample size and might have affected the ability to demonstrate non-inferiority, a preliminary analysis of this study showed that measured adherence, baseline HIV RNA concentrations, and sex, but not treatment group, were associated with virological outcome.⁷

Pharmacokinetic properties of raltegravir might have driven the findings of this study, since low trough concentrations have been associated with poorer virological outcomes. In a pharmacokinetic study of raltegravir 400 mg twice daily given with rifampicin, high intraindividual and interindividual variability was observed and the concentration of raltegravir 12 h after administration was reduced by 31%.⁶ However, no differences in virological suppression at week 24 (when the treatment of tuberculosis with rifampicin was completed) were identified between treatment groups. Furthermore, of the patients who met criteria for resistance testing in ANRS 12300 Reflate TB 2, 26 patients in the raltegravir group and 24 patients

in the efavirenz group had resistance-associated mutations, making this interpretation unlikely.

High baseline viral load might also have influenced the findings. In the STARTMRK study,³ raltegravir was effective at all baseline viral loads, whereas in the SPRING-2 study⁹ of raltegravir versus dolutegravir, a higher proportion of patients with baseline HIV RNA concentrations of more than 100 000 copies per mL had virological failure than did patients with lower baseline HIV RNA concentrations. Participants in the ANRS 12 300 Reflate TB 2 study had advanced HIV disease and we postulate that the higher baseline viral loads were associated with lower suppression rates and the difference between groups was mainly driven by participants with viral loads higher than 500 000 copies per mL at baseline. A cohort analysis of first-line INSTI use showed that despite the potency of INSTIs, virological failure was consistently associated with baseline viral load and CD4 cell count.¹⁰ INSTIs suppress viral load more quickly than NNRTIs, thus it is surprising that the difference in the proportion of participants who achieved viral suppression (HIV RNA <50 copies per mL) at week 48 was mainly accounted for by low-level viraemia (HIV RNA concentrations of 50–1000 copies per mL).

Adherence also differed between treatment groups: 94 (42%) of 230 participants in the raltegravir group had a pill count adherence ratio of less than 95% compared with 60 (27%) of 227 in the efavirenz group. Treatment adherence decreased after week 24 in both groups, perhaps due to reduced clinic attendance and support, and patient wellbeing. The raltegravir regimen provided more opportunity to be less adherent than the efavirenz regimen since participants were required to take medication three times a day (tuberculosis drugs once a day in a fasting state and the raltegravir regimen with food twice a day), whereas participants in the efavirenz group were required to take medication twice a day (tuberculosis treatment in a fasting state and the efavirenz regimen at night).

Tolerability of raltegravir is unlikely to have resulted in poor adherence since it has been shown to be well tolerated in phase 3 comparative studies. We hypothesise that high baseline viral loads and poor adherence among participants in the raltegravir group resulted in the observed difference between treatment groups.

The phase 3 ANRS 12300 Reflate TB 2 study has shown that often randomised clinical trials can lead to unanticipated results. It is imperative that treatment

of HIV-associated tuberculosis is based on data from definitive clinical trials. Rifampicin is unlikely to be replaced by another drug in the near future, thus efavirenz in combination with two nucleoside reverse transcriptase inhibitors remains the ART regimen best supported by data for use in patients with tuberculosis. Dolutegravir is the preferred INSTI for use in LMICs, with global rollout to millions of patients. If dolutegravir is used concomitantly with tuberculosis treatment, the advised dose from pharmacokinetic and phase 2 data is 50 mg twice daily¹¹ and based on the adherence observed in ANRS 12 300 Reflate TB 2, clinicians should make additional efforts to ensure adherence to this regimen.

We declare no competing interests.

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Supplementary methods

Full eligibility criteria

Inclusion criteria of the Replate TB2 trial

- Signed informed consent form
- Aged 18 years or more
- Confirmed HIV-1 infection as documented at any time prior to trial entry per national HIV testing procedures
- ART naïve
- For women of childbearing potential i.e. women of childbearing age who are not menopausal, or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) or not refraining from sexual activity: negative urinary test for pregnancy and acceptance to use contraceptive methods
- Confirmed or probable active TB disease of any location, except neurological (meningitis or encephalitis), according to the following criteria based on WHO updated definitions (see Appendix 4)
 - Bacteriologically confirmed pulmonary TB (PTB) or extrapulmonary TB (EPTB), e.g. TB with a biological specimen positive by smear microscopy, culture or nucleic acid amplification test (such as Xpert MTB/RIF)
 - Clinically diagnosed PTB or EPTB with:
 - Typical histological evidence of TB (caseous or granulomatous) on biopsy specimen or positive urinary LAM test
 - OR
 - A significant improvement on TB treatment
- Ongoing standard rifampin-containing TB treatment for ≤ 8 weeks at inclusion

Is considered a standard TB treatment a daily regimen containing rifampin, isoniazid, ethambutol and pyrazinamide for 2 months (intensive phase) followed by 4 months of daily rifampin and isoniazid (continuation phase). TB treatments with prolonged continuation phase for specific forms of EPTB, or addition of ethambutol in the continuation phase, as proposed in populations of known or suspected high levels of isoniazid resistance, are also considered standard.
- For patients in France, affiliation to a Social Security program, CMU (Universal Health Cover) or AME (State Medical Aid)³

³ Country specific for France (not to be translated): given the large proportion of beneficiaries of AME among the population usually affected by tuberculosis and HIV co-infection, it appears essential to include patients with AME

There are no inclusion criteria based on CD4 T-cell count.

Non-inclusion criteria

- HIV-2 co-infection
- Impaired hepatic function (icterus or ALT (SGPT) > 5ULN)
- Hemoglobin < 6.5 g/dL
- Creatinine clearance <60mL/min (assessed by the Cockcroft and Gault formula; see Appendix 5)
- Mycobacterium tuberculosis strain resistant to rifampin (current or past history).
 - Xpert MTB/RIF, line probe assays or culture with drug susceptibility testing (DST) can be used to assess resistance to rifampin. Probable cases of TB without drug-resistance data can be included.
- Neurological TB (meningitis or encephalitis)
- Severe associated diseases requiring specific treatment (including all specific AIDS defining illnesses other than TB, and any severe sepsis)
- Any condition which might, in the investigator's opinion, compromise the safety of treatment and/or patient's adherence to trial procedures including very severe TB-related clinical condition
- Concomitant treatments including phenytoin or phenobarbital (compounds interacting with UGT1A1)
- For HCV co-infected patients, need to start specific treatment for hepatitis during the trial duration
- For women of childbearing potential:
 - Pregnancy or breastfeeding
 - Refusal to use a contraceptive method
 - Any history of ARV intake for prevention of mother to child transmission of HIV (pMTCT)
- Subjects participating in another clinical trial evaluating therapies and including an exclusion period that is still in force during the screening phase
- Person under guardianship, or deprived of freedom by a judicial or administrative decision

Detailed follow-up

We performed clinical examination and laboratory analyses at screening, and inclusion (baseline) visits, and follow-up visits at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48.

to enable enrolment in France. In routine care, AME beneficiaries access to identical care and treatment than patients with social security or CMU.

Patients were diagnosed with confirmed or probable tuberculosis according to WHO guidelines(14), and started anti-tuberculosis treatment at clinics before referral to the trial site (14) (see supplementary appendix). Smear microscopy, Xpert® MTB/RIF (Cepheid, Sunnyvale, Ca. USA), and mycobacterial cultures results on expectorated sputum and relevant extrapulmonary samples were either collected if performed at diagnosis or obtained on newly collected at the time of tuberculosis diagnosis were collected, or samples performed at the screening visit, if not available. Chest radiographs were also performed at the screening visit, unless performed recently for tuberculosis diagnosis.

For tuberculosis follow-up, sputum smear microscopy and culture, and chest radiographs were repeated performed, per National Guidelines, and at least at week 8. Patients were tested for hepatitis B (detection of hepatitis B surface antigen), and hepatitis C (detection of hepatitis C virus specific antibodies), at the screening visit.

We measured plasma HIV-1 RNA levels at visits W0, W4, W12, W24, W32, W40, and W48 visits using the COBAS Taqman HIV-1 test assay v2.0 (Roche Diagnostics, Meylan, France) in France, Côte d'Ivoire, Mozambique, and Vietnam, and the VERSANT HIV-RNA 3.0 (bDNA) assay (Bayer, Berkeley, CA) in Brazil. We assessed presence of genotypic resistance mutations to NRTIs, NNRTIs, and integrase inhibitors in patients with virologic failure, by sequencing the reverse transcriptase and integrase genes, and reporting mutations using the consensus technique of the ANRS AC11 Resistance Group (www.hivfrenchresistance.org), both at the time of confirmed virologic failure and at baseline, using stored plasma specimens available on site.

All virology laboratories followed external quality control programs consisting in monthly HIV-1- RNA measurements on aliquots prepared by the trial central virology laboratory (Saint Louis Hospital, Paris, France) and yearly genotypic resistance tests quality controls organized by the "Centre National de Référence du VIH" in association with ANRS.

We measured CD4 cell counts at baseline, W4, W12, W24, W48 visits by flow cytometry, and we measured full blood cell counts, creatinine, and alanine aminotransferase (ALT) levels at W4, W8, W12, W24, W48 (and W2 for ALT). We performed urinary pregnancy tests at screening visits, W0, W4 visits and every follow-up visit thereafter for women of childbearing potential.

We monitored adherence to antiretroviral drugs at every follow-up visit using pill count and interviewing patients about missed doses in the past 4 days and the month prior to the visit.

Definitions

Pill count ratio

Pill count adherence ratio = (Total number of pills delivered - total number of pills returned)/total number of pills prescribed

For efavirenz the total number of pills prescribed is calculated as follows: (Last date in the trial – date of randomization) – duration of allocated treatment interruption*.

For Raltegravir, the total number of pills prescribed is calculated as follows: $2x$ [(Last date in the trial – date of randomization) – duration of allocated treatment interruption*].

*Treatment interruption is the addition of all reasons of temporary or permanent allocated treatment interruption

Pill count adherence ratio was calculated over 3 trial periods: the whole 48 weeks of follow up in the trial, the first 24 weeks (while on antituberculosis treatment), and the last 24 weeks of the trial (off anti-tuberculosis treatment).

ARV pill burden

Antiretroviral pill burden was defined as the total number of antiretroviral tablets taken while on allocated therapy (efavirenz or raltegravir) divided by the time on allocated therapy

During the trial, there were stock outs of the fixed dose combination of tenofovir/lamivudine, resulting in the prescription of lamivudine 150 mg twice daily and tenofovir disoproxil fumarate 300 mg once daily.

TB pill burden

Tuberculosis treatment pill burden was the total number of antituberculosis tablets taken between randomization and end of tuberculosis treatment divided by the time on tuberculosis treatment from randomization.

Concomitant treatment pill burden

Concomitant treatment pill burden was the total number of tablets of other treatments taken from randomization to study end divided by the time on study. If there was no data in the CRF on concomitant oral treatment taken, concomitant treatment pill burden was considered to be zero.

Statistical analysis

We described baseline characteristics in each group for the two main analysis on virologic success and optimal adherence using frequency and proportions for qualitative variables, and median and interquartile range for quantitative variables. We compared characteristics across groups using Wilcoxon tests (comparison of medians) for quantitative variables, and using the chi-squared, or the Fisher's exact test for qualitative variables as appropriate.

We used logistic regression to study determinants of virologic success and optimal adherence in 2 separate analyses. We selected variables based on previous evidence from the literature and clinical relevance. We included in the virologic success analysis as explanatory variables pill count adherence ratio $\geq 95\%$ between week 0 and week 48, baseline HIV-RNA, treatment arm, country, sex, age, BMI and CD4. We included in the optimal adherence analysis as explanatory variable the antiretroviral treatment pill burden, country, sex, age, BMI and alcohol status. We included in the multivariate model variables that were significantly associated to the dependent variable with a level of significance $p=0.25$ in univariate analysis. We derived a final model which resulted from a stepwise descending selection retaining all variables with a level of significance $p=0.05$. We analyzed data with the SAS software (version 9.4M3).

Figure S1: study flow chart

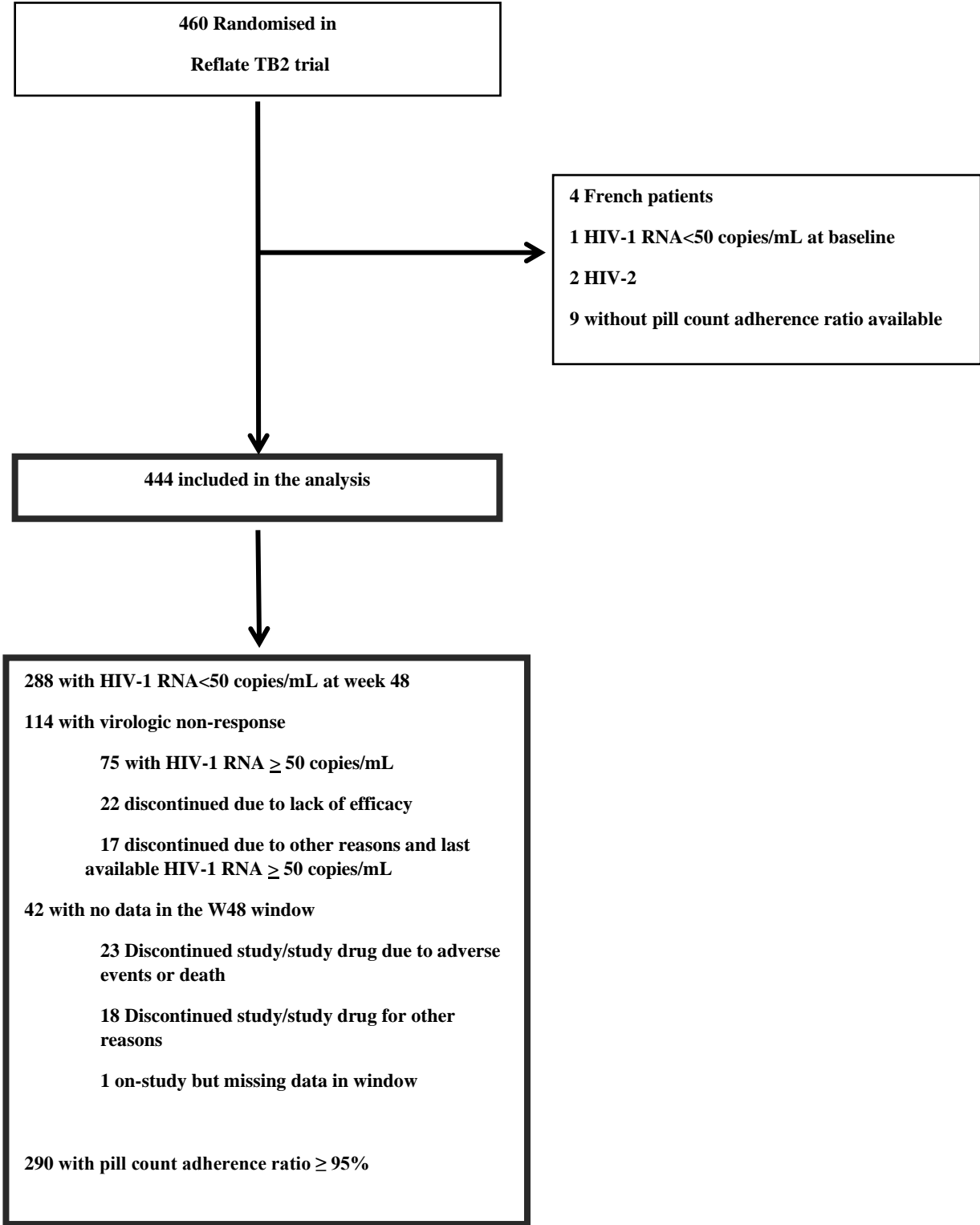
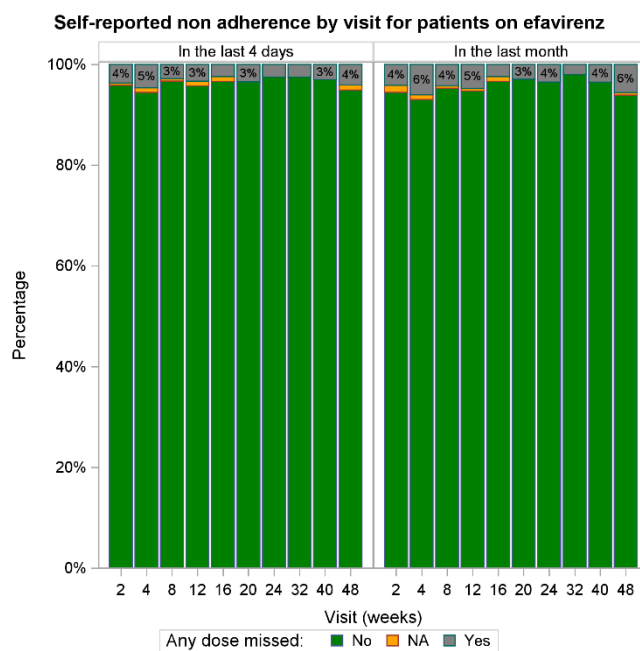


Table S1. Proportion of patients with HIV RNA-1 <200 and <1,000 copies/mL at week 48 (n=444)

Data are n (%)	Efavirenz n= 222	Raltegravir N=222)
Participants with HIV-1 RNA <200 copies per mL	163 (73%)	156 (70%)
Participants with HIV-1 RNA <1,000 copies per mL	165 (74%)	161 (73%)

Figures S2: Adherence questionnaires by treatment: proportion of patients declaring having missed at least one dose of ART



Appendix 9: Supplementary material to the publication “Differences in virologic response to antiretroviral therapy in people with HIV treated for tuberculosis in 4 high-TB burden countries – a pooled analysis of 2 randomized controlled trials.”. Submitted to AIDS

Full eligibility criteria in the ANRS 12 180 Reflate TB and ANRS 12 300 Reflate TB2 trials

- Signed informed consent form
- Aged 18 years or more
- Confirmed HIV-1 infection as documented at any time prior to trial entry per national HIV testing procedures
- HIV RNA>1,000 copies in ANRS 12180 Reflate TB trial
- ART naïve
- For women of childbearing potential i.e. women of childbearing age who are not menopausal, or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) or not refraining from sexual activity: negative urinary test for pregnancy and acceptance to use contraceptive methods
- Confirmed or probable active TB disease of any location, except neurological (meningitis or encephalitis), according to the following criteria based on WHO updated definitions (see Appendix 4)
 - Bacteriologically confirmed pulmonary TB (PTB) or extrapulmonary TB (EPTB), e.g. TB with a biological specimen positive by smear microscopy, culture or nucleic acid amplification test (such as Xpert MTB/RIF) (Xpert not available in ANRS 12 180 Reflate TB)
 - Clinically diagnosed PTB or EPTB with:
 - Typical histological evidence of TB (caseous or granulomatous) on biopsy specimen or positive urinary LAM test (LAM not available in ANRS 12 180 Reflate TB)
 - OR
 - A significant improvement on TB treatment
- Ongoing standard rifampin-containing TB treatment for ≤ 8 weeks at inclusion

Is considered a standard TB treatment a daily regimen containing rifampin, isoniazid, ethambutol and pyrazinamide for 2 months (intensive phase) followed by 4 months of daily rifampin and isoniazid (continuation phase). TB treatments with prolonged continuation phase for specific forms of EPTB, or addition of ethambutol in the continuation phase, as proposed in populations of known or suspected high levels of isoniazid resistance, are also considered standard.
- For patients in France, affiliation to a Social Security program, CMU (Universal Health Cover) or AME (State Medical Aid)⁴

⁴ Country specific for France (not to be translated): given the large proportion of beneficiaries of AME among the population usually affected by tuberculosis and HIV co-infection, it appears essential to include patients with AME

There are no inclusion criteria based on CD4 T-cell count.

Non-inclusion criteria

- HIV-2 co-infection
- Impaired hepatic function (icterus or ALT (SGPT) > 5ULN)
- Hemoglobin < 6.5 g/dL (<7 g/dL in ANRS 12180 Reflate TB)
- Creatinine clearance <60mL/min (assessed by the Cockcroft and Gault formula; see Appendix 5)
- Absolute neutrophil count of less than 750 cells per μ L, or platelet count of less than 50 000 per μ L in ANRS 12180 Reflate TB
- Mycobacterium tuberculosis strain resistant to rifampin (current or past history).

Xpert MTB/RIF, line probe assays or culture with drug susceptibility testing (DST) can be used to assess resistance to rifampin. Probable cases of TB without drug-resistance data can be included. (Xpert not available in ANRS 12 180 Reflate TB)
- Neurological TB (meningitis or encephalitis)
- Severe associated diseases requiring specific treatment (including all specific AIDS defining illnesses other than TB, and any severe sepsis)
- Any condition which might, in the investigator's opinion, compromise the safety of treatment and/or patient's adherence to trial procedures including very severe TB-related clinical condition
- Concomitant treatments including phenytoin or phenobarbital (compounds interacting with UGT1A1)
- For HCV co-infected patients, need to start specific treatment for hepatitis during the trial duration
- For women of childbearing potential:
 - Pregnancy or breastfeeding
 - Refusal to use a contraceptive method
 - Any history of ARV intake for prevention of mother to child transmission of HIV (pMTCT)
- Subjects participating in another clinical trial evaluating therapies and including an exclusion period that is still in force during the screening phase
- Person under guardianship, or deprived of freedom by a judicial or administrative decision

to enable enrolment in France. In routine care, AME beneficiaries access to identical care and treatment than patients with social security or CMU.

Figure S1: Study flow chart

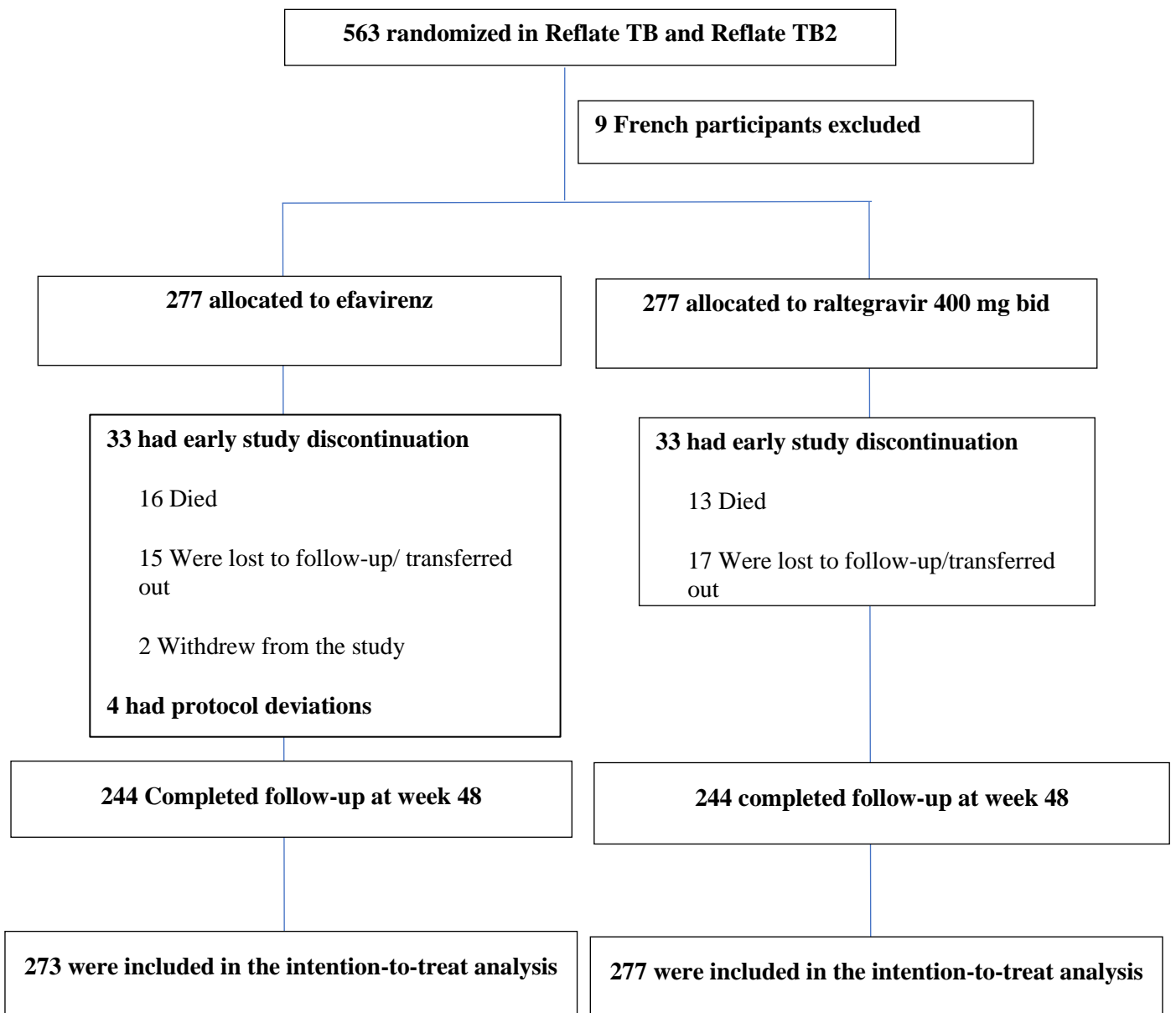


Table S1: Virologic success according to country

	TOTAL	Brazil (N=140)	Côte d'Ivoire (N=170)	Mozambique (N=129)	Vietnam (N=111)	P
Virologic success (HIV-1 RNA <50 copies per mL)	362 (65.8)	105 (75.0)	99 (58.2)	84 (65.1)	74 (66.7)	0.0217
Virologic non-response	132 (24.0)	21 (15.0)	47 (27.6)	34 (26.4)	30 (27.0)	
HIV-1 RNA ≥ 50 copies per mL	85 (15.5)	10 (7.1)	41 (24.1)	25 (19.4)	9 (8.1)	
Discontinued due to lack of efficacy	27 (4.9)	7 (5.0)	1 (0.6)	2 (1.6)	17 (15.3)	
Discontinued due to other reasons [†] and last available HIV-1 RNA ≥50 copies per mL	20 (3.6)	4 (2.9)	5 (2.9)	7 (5.4)	4 (3.6)	
No data in the week 48 window	56 (10.2)	14 (10.0)	24 (14.1)	11 (8.5)	7 (6.3)	
Discontinued study/study drug due to adverse events or death	34 (6.2)	8 (5.7)	15 (8.8)	4 (3.1)	7 (6.3)	
Discontinued study/study drug for other reasons	21 (3.8)	6 (4.3)	8 (4.7)	7 (5.4)	0	
On study but missing data in window	1 (0.2)	0	1 (0.6)	0	0	

Data are n or n (%). *95% binomial confidence interval; **Federal Drug Administration (FDA) snapshot algorithm; †Other reasons include subjects who discontinued study drug due to investigator's discretion, withdrawal of consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy.

Figure S2: Proportion of participants with HIV RNA <50 copies at each visit according to baseline HIV RNA levels in Brazil, Côte d'Ivoire, Mozambique, Vietnam

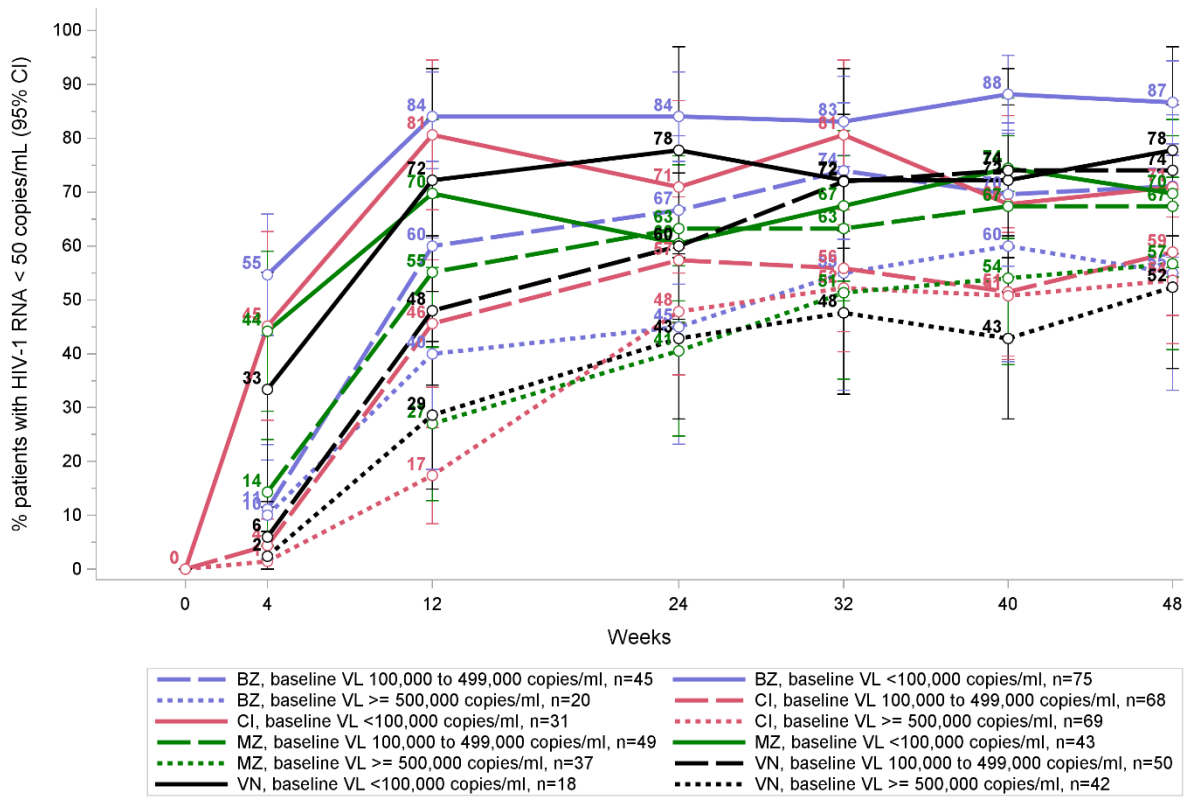


Table S2: Patients' characteristics according to treatment arm.

	N*	Efavirenz (N=273)	N*	Raltegravir (N=277)	N*	Overall (N=550)	
Female sex		102 (37.4%)		106 (38.3%)		208 (37.8%)	
Age (years)		35.7 (29.7 - 43.1)		34.4 (28.6 - 42.9)		35.4 (29.0 - 43.0)	p = 0.1380 (W)
BMI (Kg/m²)	272	19.4 (17.6 - 21.4)	276	19.4 (17.6 - 21.5)	548	19.4 (17.6 - 21.4)	p = 0.8019 (W)
CD4 (/mm³)	272	110.0 (37.5 - 242.0)		101.0 (41.0 - 234.0)	549	107.0 (40.0 - 236.0)	p = 0.6853 (W)
≤50	272	88 (32.4%)		85 (30.7%)	549	173 (31.5%)	p = 0.7189 (K)
]50 - 200]	272	95 (34.9%)		106 (38.3%)	549	201 (36.6%)	
]200 - 500]	272	89 (32.7%)		86 (31.0%)	549	175 (31.9%)	
HIV-1 RNA (log₁₀ copies/mL)		5.4 (4.9 - 5.8)	274	5.4 (4.9 - 5.7)	547	5.4 (4.9 - 5.7)	p = 0.8219 (W)
<100 000 copies/mL		85 (31.1%)	274	82 (29.9%)	547	167 (30.5%)	p = 0.7988 (K)
[100 000 - 500 000[copies/mL		102 (37.4%)	274	110 (40.1%)	547	212 (38.8%)	
≥ 500 000 copies/mL		86 (31.5%)	274	82 (29.9%)	547	168 (30.7%)	
Time since first HIV + test (days)	272	26.0 (16.5 - 38.5)	276	25.0 (16.0 - 44.5)	548	25.5 (16.0 - 41.5)	p = 0.9464 (W)
Tuberculosis presentation							
Pulmonary tuberculosis		178 (65.2%)		177 (63.9%)		355 (64.5%)	p = 0.9482 (K)
Extra pulmonary tuberculosis		47 (17.2%)		49 (17.7%)		96 (17.5%)	
Pulmonary + extrapulmonary tuberculosis		48 (17.6%)		51 (18.4%)		99 (18.0%)	
Bacteriologically confirmed tuberculosis		186 (68.1%)		180 (65.0%)		366 (66.5%)	p = 0.6655 (F)
Virologic success (HIV-1 RNA <50 copies per mL)		185 (67.9%)		177 (63.9%)		362 (65.8%)	
Virologic non response		57 (20.9%)		75 (27.1%)		132 (24.0%)	
No data in the week 48 window		31 (11.4%)		25 (9.0%)		56 (10.2%)	

Data are n (%) or median (IQR).

Table S3 : Characteristics by virologic success while on allocated therapy in patients from Brazil, Côte d'Ivoire, Mozambique and Vietnam enrolled in the Reflate TB and Reflate TB2 trial (n=550)

	N*	HIV-1 RNA <50copies/mL at W48 (N=362)	N*	HIV-1 RNA ≥50copies/mL (N=188)	
Female sex		146 (40.3)		62 (33.0)	
Country					
Brazil		105 (29.0)		35 (18.6)	
Côte d'Ivoire		99 (27.3)		71 (37.8)	
Mozambique		84 (23.2)		45 (23.9)	
Vietnam		74 (20.4)		37 (19.7)	
Age (years)		35.7 (29.6 - 43.0)		34.5 (28.4 - 43.2)	p = 0.4892 (W)
BMI (Kg/m²)	361	19.4 (17.9 - 21.6)	187	19.0 (17.3 - 20.8)	p = 0.0221 (W)
CD4 (/mm³)	361	121.0 (47.0 - 243.0)		75.0 (27.5 - 196.5)	p = 0.0039 (W)
≤50	361	105 (29.1%)		68 (36.2%)	p = 0.0370 (K)
]50 - 200]	361	128 (35.5%)		73 (38.8%)	
]200 - 500]	361	128 (35.5%)		47 (25.0%)	
Log10 HIV viral load at W0	361	5.2 (4.8 - 5.7)	186	5.6 (5.2 - 5.9)	p < 0.0001 (W)
HIV-1 RNA (copies/mL)					
<100 000 copies/mL	361	130 (36.0%)	186	37 (19.9%)	p < 0.0001 (K)
[100 000 - 500 000[copies/mL	361	142 (39.3%)	186	70 (37.6%)	
≥ 500 000 copies/mL	361	89 (24.7%)	186	79 (42.5%)	
Time since first HIV + test (days)	360	25.0 (16.0 - 42.5)		26.0 (17.0 - 40.5)	p = 0.7849 (W)
Time on TB treatment at W0 (days)		22.0 (16.0 - 34.0)		21.0 (15.0 - 31.5)	p = 0.1430 (W)
Tuberculosis presentation					
Pulmonary tuberculosis		227 (62.7%)		128 (68.1%)	p = 0.3471 (K)
Extra pulmonary tuberculosis		64 (17.7%)		32 (17.0%)	
Pulmonary + extrapulmonary tuberculosis		71 (19.6%)		28 (14.9%)	
Bacteriologically confirmed tuberculosis		239 (66.0%)		127 (67.6%)	

Data are n (%) or median (IQR).

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Titre : Efficacité d'une combinaison antirétrovirale comprenant le raltégravir pour le traitement des personnes vivant avec le VIH et traitées pour une tuberculose : mise en perspective à partir de données d'essais cliniques.

Chez les personnes vivant avec le VIH (PVVIH) et la tuberculose, la gestion du traitement antirétroviral (ARV) est complexe en raison des interactions médicamenteuses avec la rifampicine, l'un des principaux antituberculeux. L'objectif de cette thèse était d'évaluer si le raltégravir, un inhibiteur d'intégrase (INI), pourrait être proposé dans cette situation. Cette thèse s'appuie principalement sur les résultats de l'essai ANRS 12300 Reflate TB2. Il s'agissait d'un essai de phase III, en ouvert, randomisé, de non-infériorité, mené entre 2015 et 2018 au Brésil, en Côte d'Ivoire, en France, au Mozambique et au Vietnam. Au total, 460 PVVIH traités pour tuberculose et naïves de traitement antirétroviral ont reçu du raltégravir 400 mg deux fois par jour, ou de l'éfavirenz, tous deux en association avec le ténofovir et la lamivudine. À l'inclusion, la médiane de lymphocytes T CD4+ était de 103/mm³ et la médiane de charge virale VIH-1 de 5,5 Log₁₀ copies/mL. À la semaine 48, 140 (61 %) participants sous raltégravir et 150 (66 %) participants sous éfavirenz avaient un ARN VIH-1 < 50 copies/mL ; différence : -5,2 % ; IC à 95 % - 14,0 à +3,6 ; marge de non-infériorité 12 %) ; la non-infériorité n'a donc pas été démontrée. La proportion de patients avec une adhésion au traitement ARV <95% était de 43 % sous raltégravir et de 27 % sous éfavirenz (p < 0,0001). Les taux d'événements indésirables étaient similaires dans les deux bras. Pour mieux comprendre les déterminants du succès virologique et de l'adhésion aux ARV, nous avons réalisé une analyse secondaire chez 444 participants avec des données d'adhésion disponibles. Sur 48 semaines, 290/444 (65 %) participants avaient une observance ≥ 95 %. Le sexe féminin, le niveau d'ARN VIH-1 < 100.000 copies/mL à l'initiation des ARV et l'observance ≥ 95 % étaient indépendamment associés au succès virologique. Le nombre de comprimés ARV était le seul facteur associé une observance ≥ 95 %. Nous avons fusionné les données de l'essai ANRS 12180 Reflate TB (2009-2011) avec les données de l'essai ANRS 12300 Reflate TB2 afin d'analyser les différences entre pays. L'essai ANRS 12180 Reflate TB était un essai randomisé de phase II, évaluant deux doses de raltégravir et l'éfavirenz chez des PVVIH majoritairement brésiliennes avec une tuberculose. Le taux de succès virologique à la semaine 48 dans le groupe raltégravir 400 était de 76 %, similaire à celui des groupes éfavirenz ou raltégravir 800. Nous avons inclus 550 participants dans l'analyse poolée (97 de l'essai de phase II et 453 de l'essai de phase III): 140 venaient du Brésil, 170 de Côte d'Ivoire, 129 du Mozambique et 111 du Vietnam. Les médianes de charge virale à l'inclusion et les taux de succès virologique étaient respectivement 4,9, 5,6, 5,3 et 5,6 Log₁₀ copies/mL et 105/140 (75,0 %), 99/170 (58,2 %), 84/129 (65,1 %) et 74/111 (66,7 %) au Brésil, en Côte d'Ivoire, au Mozambique et au Vietnam (p<0,0001 et p=0,0217). Une charge virale < 100,000 copies était le seul facteur indépendamment associé au succès virologique. Cette analyse a également montré la non-infériorité du raltégravir par rapport à l'éfavirenz avec 177/277 (63,9%) patients sous raltégravir et 185/273 (67,8%) sous éfavirenz en succès virologique à la semaine 48 (différence -3,9% (-11,8% ; 4,1 %)). Cette thèse montre que le raltégravir pourrait être utilisé pour traiter les PVVIH ayant une tuberculose. Pour les niveaux de charge virale les plus élevés, l'efficacité virologique était inférieure à ce qui est attendu avec le raltégravir et l'éfavirenz, notamment lorsque l'observance était suboptimale. L'analyse des données des programmes de lutte contre le VIH et la tuberculose dans chaque pays est essentielle, en particulier avec le déploiement récent dans les pays à revenu faible et intermédiaire d'un autre INI, le dolutégravir.

Mots clés : VIH, tuberculose, raltégravir, traitement antirétroviral, pays du Sud

Title: Efficacy of raltegravir-based regimens for antiretroviral treatment of people with HIV and tuberculosis in low- and middle-income countries: insight from clinical trials.

In people with HIV (PWH) and tuberculosis, management of antiretroviral therapy (ART) is complex due to drug-drug interactions between antiretrovirals and rifampicin, one of the main tuberculosis drugs. The objective of this thesis was to evaluate if the integrase strand transfer inhibitor (INSTI) raltegravir could be proposed for ART in PWH treated concomitantly for tuberculosis. The thesis work is based mostly on the ANRS 12300 Reflate TB2 trial. It was an open-label, randomised, non-inferiority phase III trial, conducted between 2015 and 2018 in Côte d'Ivoire, Brazil, France, Mozambique and Vietnam. Overall, 460 ART-naïve HIV-1-infected adults with tuberculosis were randomized to receive either raltegravir 400 mg twice daily or efavirenz 600 mg once daily, both in combination with tenofovir and lamivudine. Patients' median baseline CD4+ cell count was 103/mm³ and median plasma HIV-1 RNA was 5.5 Log₁₀ copies/mL. At week 48, 140 (61%) participants on raltegravir- and 150 (66%) on efavirenz-based ART achieved virologic success (HIV-1 RNA < 50 copies/mL; difference: -5.2%; 95% CI -14.0 to +3.6; non-inferiority margin 12%), non-inferiority was not shown. The proportion of participants with sub-optimal adherence (pill count adherence ratio < 95%) was 43% on raltegravir and 27% on efavirenz (p < 0.0001). Rates of adverse events were similar in both arms. To better understand determinants of virologic success and adherence, we conducted a secondary analysis in 444 participants with adherence data available. Over 48 weeks, 290/444 (65%) participants had a pill count adherence ratio ≥ 95%. Female sex, baseline HIV-1 RNA levels < 100,000 copies/mL and pill count adherence ratio ≥ 95% were independently associated with virologic success. Antiretroviral pill burden was the only factor associated with pill count adherence ratio ≥ 95%. We pooled data from the ANRS 12180 Reflate TB phase II trial (2009-2011) with data from the ANRS 12300 Reflate TB2 trial to further explore differences between countries participating to both trials. ANRS 12180 Reflate TB trial was a multicentre, open-label, randomized, phase II trial, where 153 ART-naïve PWH with tuberculosis from Brazil or France were randomized to receive raltegravir (400 or 800 mg twice daily) or efavirenz (600 mg once daily), in combination with tenofovir and lamivudine. Virologic suppression at week 48 with raltegravir 400 mg twice daily was 76%, which was similar to efavirenz or raltegravir 800 mg twice daily. We included 550 participants (97 from the phase II and 453 from the phase III trial) in the pooled analysis: 140 from Brazil, 170 from Côte d'Ivoire, 129 from Mozambique and 111 from Vietnam. Median baseline HIV-1 RNA and virologic success rates were 4.9, 5.6, 5.3, and 5.6 Log₁₀ copies/mL and 105/140 (75.0%), 99/170 (58.2%), 84/129 (65.1%) and 74/111 (66.7%) in Brazil, Côte d'Ivoire, Mozambique and Vietnam, respectively (p < 0.0001 and p = 0.0217). Lower baseline HIV-1 RNA was the only factor independently associated with virologic success. This analysis also showed the non-inferiority of raltegravir compared to efavirenz at week 48 with 177/277 (63.9%) patients on raltegravir and 185/273 (67.8%) on efavirenz achieved virologic success (difference -3.9% (-11.8%; 4.1%)). This thesis shows that raltegravir-based ART could be used to treat PWH with tuberculosis. However, in participants with high HIV RNA, virologic efficacy rates were lower than expected both with raltegravir and efavirenz, especially when adherence was suboptimal. Further analyzing data from national HIV and tuberculosis programs on virologic success rates in PWH with tuberculosis is therefore key, especially with the recent roll out of the second generation INSTI dolutegravir in low- and middle-income countries.

Keywords: HIV, tuberculosis, raltegravir, antiretroviral treatment, LMICs

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