Enseignements dirigés de lecture critique d'article

Plutôt bictegravir ou dolutegravir ?

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- Etude de non-infériorité …

Quel journal???

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- Lancet : impact factor 2021 = 79,321

- Impact factor = nbre moy de citations par article pendant 2 ans

Contexte

- Traitements anti-VIH au moment de l’étude

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  - 2 inhibiteurs nucléos(t)idiques + inhibiteur d'intégrase

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- 3 inhibiteurs d'intégrase disponibles
  - Raltégravir
  - Elvitégravir
  - Dolutégravir

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  - 2 inhibiteurs nucléos(t)idiques + inhibiteur d'intégrase
- 3 inhibiteurs d'intégrase disponibles
  - Raltégravir
  - Elvitégravir
  - Dolutégravir
- Intérêt d'un nouvel inhibiteur d'intégrase?

Méthodologie

- Design et critères d'inclusion/exclusion

- Méthode de randomisation

Méthodologie

- Design et critères d'inclusion/exclusion
  - Essai de phase III, randomisé, double-aveugle, multicentrique, international, contrôlé, de non-infériorité
  - Inclusion: adultes, HIV RNA level>500 cp/mL, eGFR>30 mL/min, absence de résistance sur la transcriptase inverse
  - HCV et HBV autorisés
- Méthode de randomisation
  - Randomisation 1:1 (sur CV, CD4, région)

Déclaration d’Helsinki

Déclaration d'Helsinki

- Document de l'association médicale mondiale
- Principes éthiques pour la recherche médicale
- Première version de 1964
- Dernière mise à jour à Fortaleza en 2013

https://www.wma.net/fr/policies-post/declaration-dhelsinki-de-lamm-principes-ethiques-applicables-a-la-recherche-medicale-impliquant-des-etres-humains/

Méthodologie

- Critère de jugement principal

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  - HIV1 RNA < 50 cp/mL à W48 en snapshot

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- Critères secondaires de jugement

Méthodologie

- Critère de jugement principal
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- Critères secondaires de jugement
  - Stratification (âge, sexe, origine, HIV RNA de départ, CD4 de départ, région, observance)
  - Données manquantes = échec versus données manquantes = exclusion
  - Tolérance (glycémie, lipides, eGFR)

Méthodologie

- Intention de traiter

- Per-protocole

Méthodologie

- Intention de traiter
  - Analyse de tous les patients traités
  - Référence pour les essais de supériorité
  - Minimise les différences entre les 2 groupes

- Per-protocole
  - Analyse des patients ayant rempli les obligations du protocole
  - Référence pour les essais de non-infériorité
  - Maximise les différences entre les 2 groupes

Méthodologie

- Analyse statistique
  - Sur le critère de jugement principal
  - Sur le calcul du nombre de sujet

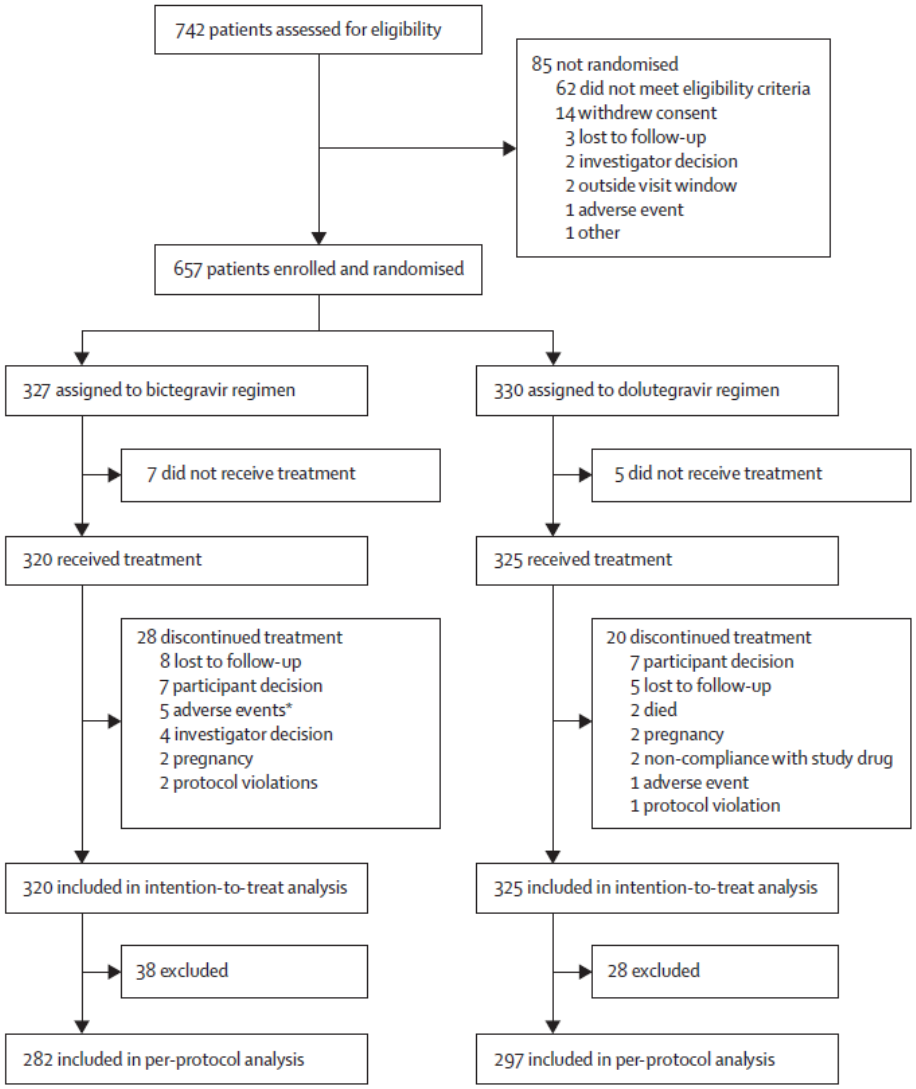
Méthodologie

- Analyse statistique
  - Sur le critère de jugement principal
    - Marge de non-infériorité: 12% (FDA, CI:95%)
  - Sur le calcul du nombre de sujet
    - Efficacité envisagée: 91% sur le critère de jugement principal
    - Puissance: 95%
    - α: 2,5% one-sided

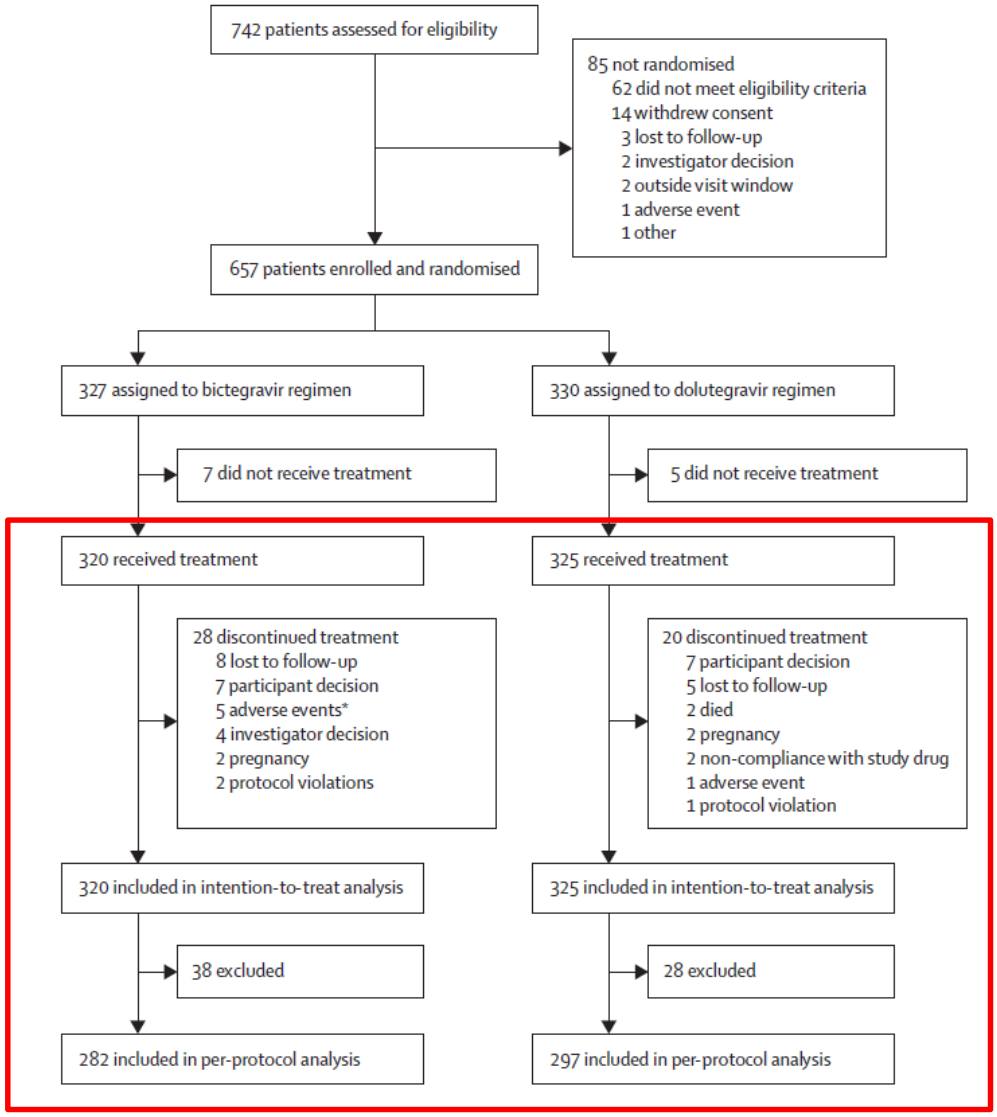
Méthodologie

- Analyse statistique
  - Sur le critère de jugement principal
    - Marge de non-infériorité: 12% (FDA, CI:95%)
  - Sur le calcul du nombre de sujet
    - Efficacité envisagée: 91% sur le critère de jugement principal
    - Puissance: 95% (1-β où β est le risque de ne pas conclure à une non-infériorité alors qu'elle existe)
    - α: 2,5% one-sided (α est le risque de conclure à une non-infériorité qui n'existe pas)

Profil de l'essai (flowchart)



Profil de l'essai (flowchart)



	Bictegravir regimen (n=320)	Dolutegravir regimen (n=325)
Median age, years	33 (27–46)	34 (27–46)
Sex		
Women	40 (13%)	37 (11%)
Men	280 (88%)	288 (89%)
Race		
White	183 (57%)	195 (60%)
Black	97 (30%)	100 (31%)
Asian	7 (2%)	10 (3%)
Ethnic origin		
Hispanic or Latino	83 (26%)	81 (25%)
Region		
USA	193 (60%)	193 (59%)
Outside the USA	127 (40%)	132 (41%)
HIV disease status		
Asymptomatic	286 (89%)	288 (89%)
Symptomatic	10 (3%)	11 (3%)
AIDS	24 (8%)	26 (8%)
HIV risk factor*		
Heterosexual sex	81 (25%)	77 (24%)
Homosexual sex	237 (74%)	250 (77%)
Intravenous drug use	3 (1%)	6 (2%)
Median HIV-1 RNA $\log_{10}$ copies per mL	4·43 (3·95–4·90)	4·45 (4·03–4·84)
HIV-1 RNA concentration		
>100 000 to ≤400 000 copies per mL	54 (17%)	41 (13%)
>400 000 copies per mL	12 (4%)	13 (4%)
Median CD4 count (cells per µL)	440 (289–591)	441 (297–597)
CD4 count (cells per µL)		
<50	15 (5%)	13 (4%)
≥50 to <200	29 (9%)	21 (6%)
≥200 to <350	67 (21%)	77 (24%)
≥350 to <500	91 (28%)	94 (29%)
≥500	118 (37%)	120 (37%)
Median creatinine clearance (mL/min)	120·4 (100·8–141·8)	120·6 (102·8–145·1)
Patients with HIV/HBV co-infection	8 (3%)	6 (2%)
Patients with HIV/HCV co-infection	5 (2%)	5 (2%)
Median body-mass index (kg/m²)	25·0 (22·2–28·3)	24·6 (22·2–28·0)

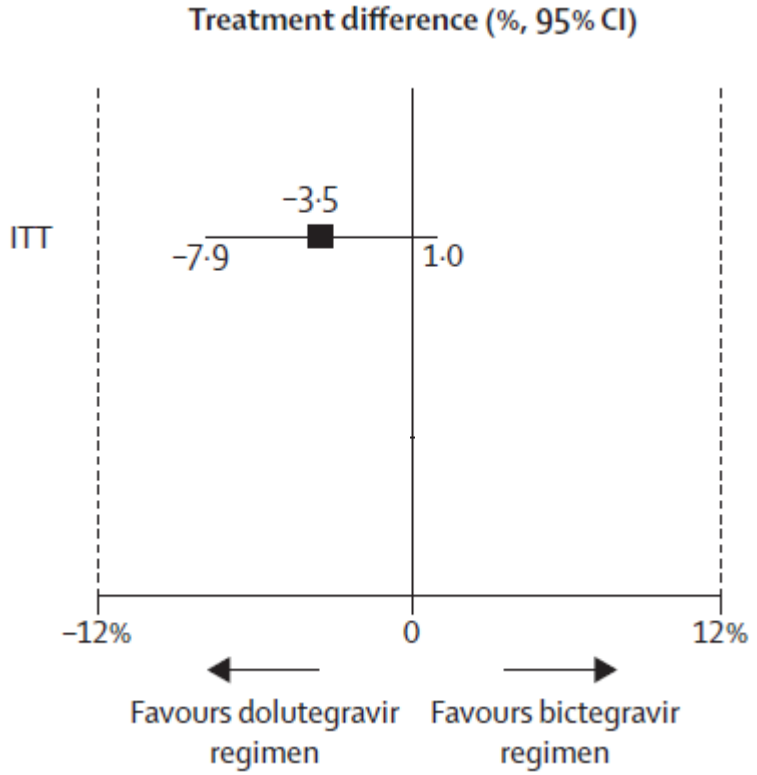
Data are median (IQR) or n (%), except for age, which is median (range).
*A participant may fit more than one HIV risk factor category; therefore, percentages may add to more than 100%. HBV=hepatitis B virus. HCV=hepatitis C virus.

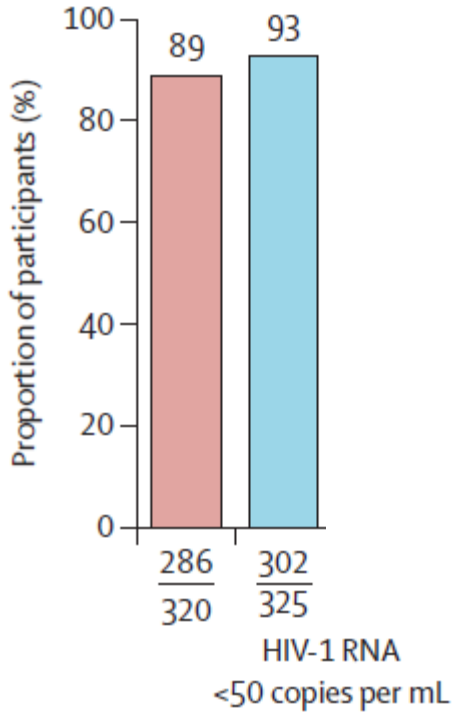
Table 1: **Baseline demographic and clinical characteristics**

Population de départ

Résultats

- Sur le critère de jugement principal
  - Non-infériorité du bictegravir versus dolutegravir





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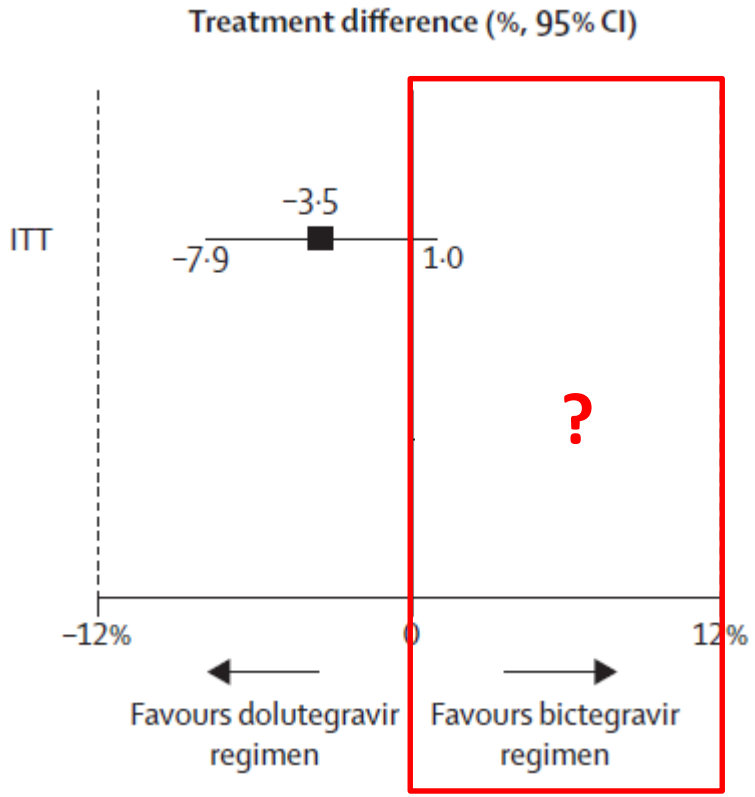

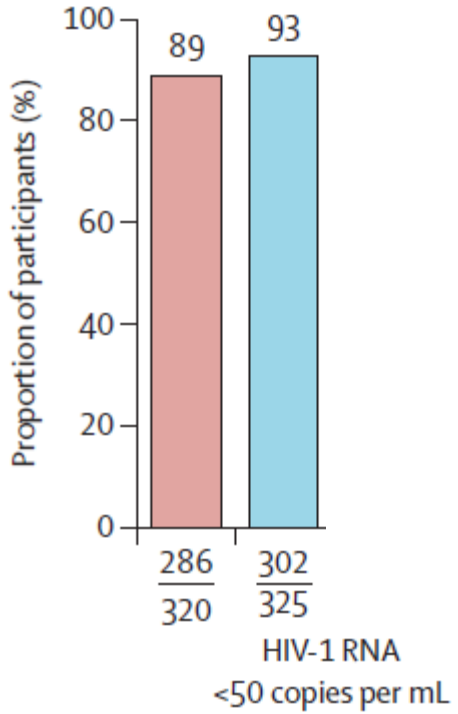

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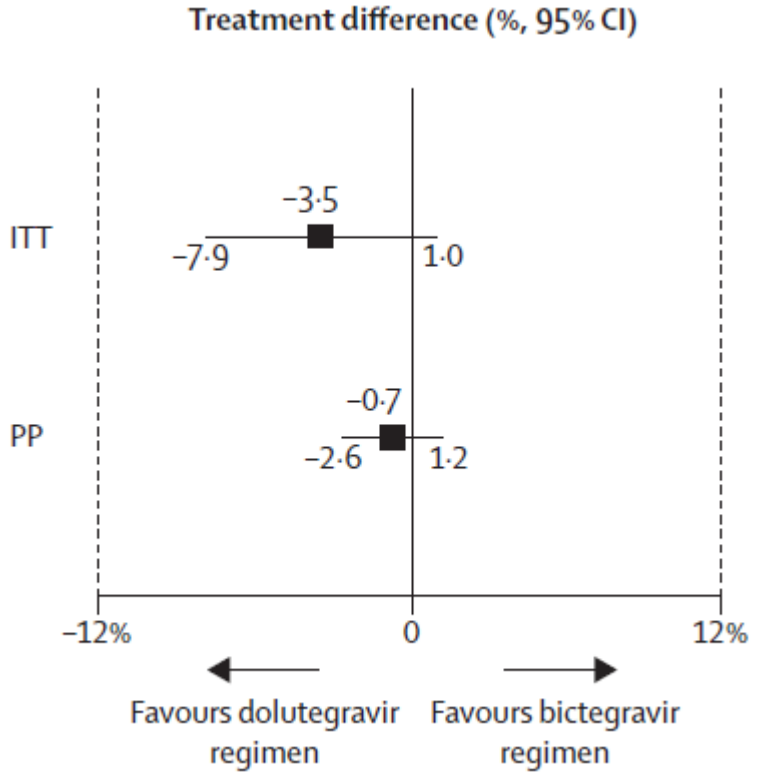

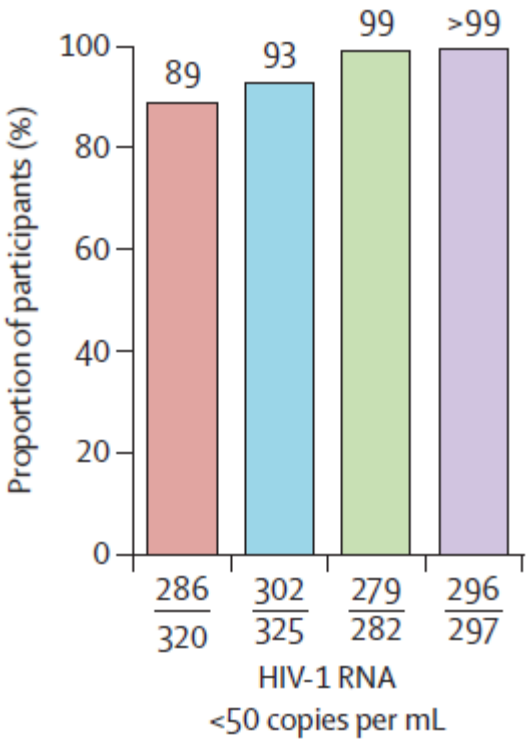

Résultats

- Sur les critères secondaires
  - Non-infériorité sur la CV

	Bictegravir regimen (n=320)	Dolutegravir regimen (n=325)	p value*	Treatment difference (95% CI)†
HIV-1 RNA <50 copies per mL	286 (89%)	302 (93%)	0·12	−3·5% (−7·9 to 1·0)
HIV-1 RNA ≥50 copies per mL	14 (4%)	4 (1%)		
HIV-1 RNA ≥50 copies per mL	3 (1%)	1 (<1%)		
Discontinued due to lack of efficacy	0	0		
Discontinued due to other reasons‡ and last available HIV-1 RNA ≥50 copies per mL	11 (3%)	3 (1%)		
No virological data	20 (6%)	19 (6%)		
Discontinued due to adverse events or death	3 (1%)	3 (1%)		
Discontinued due to other reasons‡ and last available HIV-1 RNA <50 copies per mL	11 (3%)	14 (4%)		
Missing data but on study drug	6 (2%)	2 (1%)		

Résultats

- Sur les sorties d'étude

	Bictegravir regimen (n=320)	Dolutegravir regimen (n=325)	p value*	Treatment difference (95% CI)†
HIV-1 RNA <50 copies per mL	286 (89%)	302 (93%)	0·12	−3.5% (−7·9 to 1·0)
HIV-1 RNA ≥50 copies per mL	14 (4%)	4 (1%)		
HIV-1 RNA ≥50 copies per mL	3 (1%)	1 (<1%)		
Discontinued due to lack of efficacy	0	0		
Discontinued due to other reasons‡ and last available HIV-1 RNA ≥50 copies per mL	11 (3%)	3 (1%)		
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Discontinued due to adverse events or death	3 (1%)	3 (1%)		
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Résultats

- Sur la tolérance

	Bictegravir regimen (n=320)	Dolutegravir regimen (n=325)
Adverse event ≥5%		
Headache	40 (13%)	40 (12%)
Diarrhoea	37 (12%)	39 (12%)
Nausea	25 (8%)	29 (9%)
Nasopharyngitis	22 (7%)	31 (10%)
Fatigue	19 (6%)	26 (8%)
Upper respiratory tract infection	15 (5%)	23 (7%)
Lymphadenopathy	17 (5%)	18 (6%)
Pyrexia	14 (4%)	21 (6%)
Back pain	11 (3%)	20 (6%)
Insomnia	16 (5%)	14 (4%)
Influenza	17 (5%)	10 (3%)
Arthralgia	16 (5%)	9 (3%)

Data are n (%).

Table 3: Adverse events

Indépendance de l’étude ?

Indépendance de l'étude ?

Paul E Sax, Anton Pozniak, M Luisa Montes, Ellen Koenig, Edwin DeJesus, Hans-Jürgen Stellbrink, Andrea Antinori, Kimberly Workowski, Jihad Slim, Jacques Reynes, Will Garner, Joseph Custodio, Kirsten White, Devi SenGupta, Andrew Cheng, Erin Quirk

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing the report. The corresponding author (DS) had full access to all the data in the study. PES, DS, EQ, and AC had final responsibility for the decision to submit the manuscript for publication.

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Indépendance de l'étude ?

- Indépendance de cet enseignement dirigé …

https://www.transparence.sante.gouv.fr

Dans la peau de la commission de transparence de la HAS

- SMR ?
- ASMR ?

En résumé…

En résumé…

Summary

Background Integrase strand transfer inhibitors (INSTIs) coadministered with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) are recommended as first-line treatment for HIV, and coformulated fixed-dose combinations are preferred to facilitate adherence. We report 48-week results from a study comparing initial HIV-1 treatment with bictegravir—a novel INSTI with a high in-vitro barrier to resistance and low potential as a perpetrator or victim of clinically relevant drug interactions—coformulated with the NRTI combination emtricitabine and tenofovir alafenamide as a fixed-dose combination to dolutegravir administered with coformulated emtricitabine and tenofovir alafenamide.

Methods In this randomised, double-blind, multicentre, placebo-controlled, non-inferiority trial, HIV-infected adults were screened and enrolled at 126 outpatient centres in 10 countries in Australia, Europe, Latin America, and North America. Participants were previously untreated adults (HIV-1 RNA ≥500 copies per mL) with estimated glomerular filtration rate of at least 30 mL/min. Chronic hepatitis B virus or hepatitis C co-infection was allowed. We randomly assigned participants (1:1) to receive oral fixed-dose combination bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg or dolutegravir 50 mg with coformulated emtricitabine 200 mg and tenofovir alafenamide 25 mg, with matching placebo, once a day for 144 weeks. Investigators, participants, study staff, and those assessing outcomes were masked to treatment group. All participants who received at least one dose of study drug were included in primary efficacy and safety analyses. The primary endpoint was the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 (US Food and Drug Administration snapshot algorithm), with a prespecified non-inferiority margin of –12%. This study is registered with ClinicalTrials.gov, number NCT02607956.

Findings Between Nov 11, 2015, and July 15, 2016, 742 participants were screened for eligibility, of whom 657 were randomly assigned to treatment (327 with bictegravir, emtricitabine, and tenofovir alafenamide fixed-dose combination [bictegravir group] and 330 with dolutegravir plus emtricitabine and tenofovir alafenamide [dolutegravir group]). 320 participants who received the bictegravir regimen and 325 participants who received the dolutegravir regimen were included in the primary efficacy analyses. At week 48, HIV-1 RNA <50 copies per mL was achieved in 286 (89%) of 320 participants in the bictegravir group and 302 (93%) of 325 in the dolutegravir group (difference –3·5%, 95·002% CI –7·9 to 1·0, p=0·12), showing non-inferiority of the bictegravir regimen to the dolutegravir regimen. No treatment-emergent resistance to any study drug was observed. Incidence and severity of adverse events were similar between groups, and few participants discontinued treatment due to adverse events (5 [2%] of 320 in the bictegravir group and 1 [<1%] 325 in the dolutegravir group). Study drug-related adverse events were less common in the bictegravir group than in the dolutegravir group (57 [18%] of 320 *vs* 83 [26%] of 325, p=0·022).

Interpretation At 48 weeks, virological suppression with the bictegravir regimen was achieved and was non-inferior to the dolutegravir regimen in previously untreated adults. There was no emergent resistance to either regimen. The fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide was safe and well tolerated compared with the dolutegravir regimen.

Funding Gilead Sciences Inc.