Efficacy and safety of three antiretroviral therapy regimens for treatment-naive African adults living with HIV-2 (FIT-2): a pilot, phase 2, non-comparative, open-label, randomised controlled trial

Serge P Eholie, Didier K Ekouevi, Corine Chazallon, Charlotte Charpentier, Eugène Messou, Zelica Diallo, Jacques Zoungrana, Albert Minga, Ndeye Fatou Ngom Gueye, Denise Hawerlander, Fassery Dembele, Géraldine Colin, Boris Tchounga, Sophie Karcher, Jérome Le Carrou, Annick Tchabert-Guié, Thomas-d'Aquin Toni, Abdoul-Salam Ouédraogo, Guillaume Bado, Coumba Toure Kane, Moussa Seydi, Armel Poda, Ephrem Mensah, Illah Diallo, Youssouf Joseph Drabo, Xavier Anglaret, Françoise Brun-Vezinet*, for the FIT-2 study group†*

Lancet HIV 2024; 11: e380–88

Published Online May 10, 2024 https://doi.org/10.1016/S2352-3018(24)00085-7

See Comment page e347

*Contributed equally

†Study group members are listed in the appendix (pp 3–4)

Université Félix Houphouët-Boigny, Département de Dermatologie et d'Infectiologie, UFR des Sciences Médicales, Abidjan, Côte d'Ivoire (S P Eholie MD, Z Diallo MPH); **Centre Hospitalier Universitaire de Treichville Service des Maladies Infectieuses et Tropicales, Abidjan, Côte d'Ivoire** (S P Eholie, Z Diallo); **Programme PACCI, Abidjan, Côte d'Ivoire** (S P Eholie, D K Ekouevi PhD, C Chazallon MSc, Z Diallo, G Colin MPH, B Tchounga PhD, S Karcher MSc, J Le Carrou PhD, A Tchabert-Guié MD PhD, T-d'A Toni PhD, X Anglaret PhD); **University of Bordeaux, National Institute for Health and Medical Research (INSERM) UMR 1219, Research Institute for Sustainable Development (IRD) EMR 271, Bordeaux Population Health Research Centre, Bordeaux, France** (D K Ekouevi, C Chazallon, G Colin, B Tchounga, S Karcher, J Le Carrou, X Anglaret); **Centre Africain de Recherche en Epidémiologie et en Santé Publique, Lomé, Togo** (D K Ekouevi); **Université de Lomé, Département Santé Publique, Lomé, Togo** (D K Ekouevi); **Service de virologie, Université Paris Cité, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France** (C Charpentier PhD,

Summary

Background Due to the low number of individuals with HIV-2, no randomised trials of HIV-2 treatment have ever been done. We hypothesised that a non-comparative study describing the outcomes of several antiretroviral therapy (ART) regimens in parallel groups would improve understanding of how differences between HIV-1 and HIV-2 might lead to different therapeutic approaches.

Methods This pilot, phase 2, non-comparative, open-label, randomised controlled trial was done in Burkina Faso, Côte d'Ivoire, Senegal, and Togo. Adults with HIV-2 who were ART naive with CD4 counts of 200 cells per µL or greater were randomly assigned 1:1:1 to one of three treatment groups. A computer-generated sequentially numbered block randomisation list stratified by country was used for online allocation to the next available treatment group. In all groups, tenofovir disoproxil fumarate (henceforth tenofovir) was dosed at 245 mg once daily with either emtricitabine at 200 mg once daily or lamivudine at 300 mg once daily. The triple nucleoside reverse transcriptase inhibitor (NRTI) group received zidovudine at 250 mg twice daily. The ritonavir-boosted lopinavir group received lopinavir at 400 mg twice daily boosted with ritonavir at 100 mg twice daily. The raltegravir group received raltegravir at 400 mg twice daily. The primary outcome was the rate of treatment success at week 96, defined as an absence of serious morbidity event during follow-up, plasma HIV-2 RNA less than 50 copies per mL at week 96, and a substantial increase in CD4 cells between baseline and week 96. This trial is registered at ClinicalTrials.gov, NCT02150993, and is closed to new participants.

Findings Between Jan 26, 2016, and June 29, 2017, 210 participants were randomly assigned to treatment groups. Five participants died during the 96 weeks of follow-up (triple NRTI group, n=2; ritonavir-boosted lopinavir group, n=2; and raltegravir group, n=1), eight had a serious morbidity event (triple NRTI group, n=4; ritonavir-boosted lopinavir group, n=3; and raltegravir group, n=1), 17 had plasma HIV-2 RNA of 50 copies per mL or greater at least once (triple NRTI group, n=11; ritonavir-boosted lopinavir group, n=4; and raltegravir group, n=2), 32 (all in the triple NRTI group) switched to another ART regimen, and 18 permanently discontinued ART (triple NRTI group, n=5; ritonavir-boosted lopinavir group, n=7; and raltegravir group, n=6). The Data Safety Monitoring Board recommended premature termination of the triple NRTI regimen for safety reasons. The overall treatment success rate was 57% (95% CI 47–66) in the ritonavir-boosted lopinavir group and 59% (49–68) in the raltegravir group.

Interpretation The raltegravir and ritonavir-boosted lopinavir regimens were efficient and safe in adults with HIV-2. Both regimens could be compared in future phase 3 trials. The results of this pilot study suggest a trend towards better virological and immunological efficacy in the raltegravir-based regimen.

Funding ANRS MIE.

Copyright © 2024 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

Introduction

HIV-2 is an enveloped retrovirus with an endemic area concentrated mainly in west Africa, and a lesser spread to other parts of the world.[1] The estimated number of people with HIV-2 worldwide is between 1 and 2 million.[2] HIV-2 has a lower replicative capacity than HIV-1, which has important clinical consequences including lower risk of vertical transmission during pregnancy and lactation, and slower progression to immunosuppression and its associated risk of serious complications. When immunosuppression occurs, it presents the same characteristics as those associated

Research in context

Evidence before this study

We searched PubMed on June 30, 2023, with no date restrictions, using the terms "HIV-2" AND "randomised controlled trial" OR "cohort", with no language or date restrictions. No randomised controlled trials were identified. We found five non-randomised prospective studies that reported the efficacy of antiretroviral therapy (ART) in individuals with HIV-2, suggesting that ritonavir-boosted lopinavir was the most suitable protease inhibitor in HIV-2 infection and that integrase strand transfer inhibitors (known as INSTIs) were a promising alternative to anti-HIV-2 drugs.

Added value of this study

To our knowledge, this study is the first randomised controlled trial on the efficacy and tolerance of three first-line ART regimens in adults with HIV-2. All regimens included tenofovir and emtricitabine or lamivudine. The third drug was either zidovudine (triple nucleoside reverse transcriptase inhibitor [NRTI] regimen), ritonavir-boosted lopinavir, or raltegravir depending on group assignment. The data suggest that the triple NRTI regimen should not be used, and that the ritonavir-boosted lopinavir and raltegravir-based regimens both have good efficacy and tolerance and could be further assessed in phase 3 trials. The study also provides evidence on the efficacy endpoints for use in future trials. Due to the low replicative capacity of HIV-2, nearly 100% of the participants with HIV-2 in future studies would have an unquantifiable viral load under treatment, with a threshold of 50 copies per mL. A much lower level of viraemia should be considered. CD4 cell count gain under treatment seems to be an interesting criterion, including in individuals with more than 500 CD4 cells per µL, but it remains difficult to set a discriminating gain threshold for the definition of success or failure. Finally, permanent discontinuation of ART appears to be a non-discriminatory but rather frequent phenomenon, perhaps reflecting the possibility that individuals with HIV-2 and their treating physicians do not have a clear idea of the benefit–risk ratio of ART for everyone regardless of CD4 cell count, which is now universally accepted practice for HIV-1.

Implications of all the available evidence

Both the ritonavir-boosted lopinavir and raltegravir regimens are suitable for the first-line treatment of HIV-2. Raltegravir-based regimens tend to have better virological and immunological benefits, but the overall benefit–risk ratios of the two regimens are still to be compared in a phase 3 randomised controlled trial.

with HIV-1 in terms of type and severity of opportunistic diseases.[3–6]

HIV-2 and HIV-1 differ in terms of phenotypic susceptibility to antiretrovirals. HIV-2 has long been known to be intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs).[7,8] The natural resistance of HIV-2 to fusion inhibitors has been described recently,[9] with phenotypic studies suggesting that saquinavir, lopinavir, and darunavir are the only effective protease inhibitors against HIV-2, and two single-arm trials suggesting that integrase strand transfer inhibitors (INSTIs) are promising anti-HIV-2 drugs.[9–13] However, due to HIV-2 being concentrated in west Africa and the low number of people affected, no randomised trials comparing antiretroviral therapy (ART) regimens in people with HIV-2 have ever been done.[14–18]

A phase 3 efficacy trial comparing the reference treatment of HIV-2 to alternative treatments would require a high number of participants, which is difficult to achieve for such a rare disease. Any trial would also rely on a fragile pre-trial hypothesis because of the absence of previous randomised evidence. Before embarking on a long and expensive project, gathering solid preliminary data was necessary. We hypothesised that a non-comparative pilot study describing the evolution of clinical, immunological, and virological outcomes under several ART regimens in small parallel groups would help to better design future large-scale comparative trials and to understand how differences between HIV-1 and HIV-2 might require different therapeutic approaches in terms of drug choice but also in terms of criteria for starting treatment and for assessing the success of treatment.

Methods

Study design

FIT-2 ANRS 12294 was a pilot, phase 2, non-comparative, open-label, randomised controlled trial, conducted at seven HIV care centres in four countries: Burkina Faso (Ouagadougou and Bobo-Dioulasso), Côte d'Ivoire (Abidjan), Senegal (Dakar), and Togo (Lomé). The study was approved by the national ethics committees of the four countries. The protocol is available in the appendix (pp 10–82). This trial is registered at ClinicalTrials.gov, NCT02180438.

Participants

For inclusion, participants had to have HIV-2 (as diagnosed using the FIT-2 serological test algorithm; appendix p 7), no previous history of ART, a CD4 count greater than 200 cells per µL, were required to be aged 18 years and older, and had to provide written informed consent.

The main exclusion criteria were HIV-1 and HIV-2 dual infection, pregnancy or breastfeeding, severe anaemia (haemoglobin ≤8 g/dL), neutropenia (neutrophils ≤500 cells per µL) or thrombocytopenia

F Brun-Vezinet PhD); **Centre de Prise en Charge et de Formation (CePReF), Abidjan, Côte d'Ivoire** (E Messou PhD); **Service des Maladies Infectieuses et Tropicales, CHU Sourô Sanou, Bobo-Dioulasso, Burkina-Faso** (J Zoungrana MD, A Poda MD); **Centre Médical de Suivi des Donneurs de Sang (CMSDS-CNTSCI), Abidjan, Côte d'Ivoire** (A Minga MPH); **Service des Maladies Infectieuses et Tropicales, CHNU Fann, Dakar, Sénégal** (N F Ngom Gueye MD, M Seydi MD); **Centre Intégré de Recherches Biocliniques d'Abidjan (CIRBA) Abidjan, Côte d'Ivoire** (D Hawerlander MD); **Unité de soins ambulatoires et de conseil (USAC), CHU de Treichville, Abidjan, Côte d'Ivoire** (F Dembele MD); **CeDReS, Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire** (T-d'A Toni); **Unité de Virologie, CHU Sourô Sanou, Bobo-Dioulasso, Burkina-Faso** (A-S Ouédraogo PhD, G Bado PharmD); **Laboratoire de Bacteriologie, Virologie, CHU Le Dantec, Dakar, Sénégal** (C Toure Kane PharmD); **ONG espoir Vie Togo, Cente Medico-social, Licia Lomé, Togo** (E Mensah MD); **Service de Médecine Interne, CHU Yalgado OUEDRAOGO, Ouagadougou, Burkina Faso** (I Diallo MD, Y J Drabo MD)

Correspondence to:
Dr Xavier Anglaret, University of Bordeaux, National Institute for Health and Medical Research (INSERM) UMR 1219, Research Institute for Sustainable Development (IRD) EMR 271, Bordeaux Population Health Research Centre, Bordeaux 33076, France
xavier.anglaret@u-bordeaux.fr

See **Online** for appendix

(platelet ≤50 000 per µL), renal impairment (creatinine clearance ≤50 mL per min), liver function impairment (prothrombin time <50%), non-stabilised ongoing severe illness, conditions favouring one ART regimen over the others, and known contraindication to a trial drug (appendix p 28).

Randomisation and masking

Eligible participants were randomly assigned 1:1:1 to one of the three following ART regimens: tenofovir disoproxil fumarate (henceforth tenofovir), emtricitabine or lamivudine, and zidovudine (the triple nucleoside reverse transcriptase inhibitor [NRTI] group); tenofovir, and emtricitabine or lamivudine, and ritonavir-boosted lopinavir (ritonavir-boosted lopinavir group); or tenofovir, and emtricitabine or lamivudine, and raltegravir (raltegravir group). A computer-generated sequentially numbered block randomisation list stratified by country was fed into an in-house software programme by an engineer who had no involvement in the rest of the trial for online allocation to the next available treatment group, concealing the sequence until interventions were assigned.

Procedures

In all groups, tenofovir was dosed at 245 mg once daily, with either emtricitabine at 200 mg once daily or lamivudine at 300 mg once daily. For the triple NRTI group, zidovudine was given at 250 mg twice daily; for the ritonavir-boosted lopinavir group, lopinavir was given at 400 mg twice daily and boosted with ritonavir at 100 mg twice daily; for the raltegravir group, raltegravir was given at 400 mg twice daily.

Co-trimoxazole prophylaxis was prescribed to all patients with a CD4 count less than 500 cells per µL.

The participants were monitored for 96 weeks from the start of ART. Visits to the study clinic were scheduled every 4 weeks up to week 24 and every 12 weeks thereafter, and the patients were instructed to report to the clinic between visits if they had any clinical problems.

CD4 cell count and plasma HIV-2 RNA were measured at inclusion (day 0) and weeks 4, 8, 12, 24, 36, 48, 72, and 96. CD4 cell count was measured using a fluorescence-activated cell sorting (known as FACS) count flow cytometer (Fascan Becton-Dickinson, San Carlos, CA, USA). HIV-2 RNA was measured using a real-time PCR assay (Generic HIV-2 Charge Virale Biocentric, Bandol, France; with a limit of detection [LOD] of 10 copies per mL and limit of quantification [LOQ] of 50 copies per mL).[19]

Blood samples were taken by trained nurses. Whole blood was stored at –80°C for further HIV-2 total DNA quantification. Total DNA was extracted using a QIAsymphony DSP DNA mini kit (Qiagen, Courtaboeuf, France). To normalise the HIV-2 DNA quantification, the amount of total DNA in extracts was identified by quantification of the albumin gene, using a LightCycler FastStart DNA Master Hybprobe kit (Roche, Mannheim, Germany), and serial dilutions of Human Genomic DNA (Roche, Mannheim, Germany) as standard.[20,21] HIV-2 total DNA was quantified using a real-time PCR assay with a 95% LOD of 3 copies per PCR and LOQ of 6 copies per PCR.[22]

Genotypic resistance tests were carried out each time two consecutive plasma HIV-2 RNAs were 50 copies per mL or greater. Sequencing of protease, reverse transcriptase, and integrase regions was carried out using previously described in-house methods.[19] HIV-2 drug resistance mutations were classified using the list from The Collaborative HIV and Anti-HIV Drugs Resistance Network.[23]

HIV-2 RNA was measured at the virology laboratories of the Treichville hospital in Abidjan (Côte d'Ivoire, for samples from Togo and Côte d'Ivoire), Le Dantec hospital in Dakar (Senegal) for samples from Senegal, and Souro Sanou hospital in Bobo-Dioulasso (Burkina Faso) for samples from Burkina Faso. The HIV-2 RNA measurement protocol was harmonised across laboratories, and a quality control process was carried out in the three laboratories under the supervision of the virology laboratory of the Bichat-Claude Bernard hospital (Paris, France). HIV-2 DNA measurement and RNA genotypic resistance tests were carried out at the virology laboratory of Bichat-Claude Bernard hospital.

Outcomes

The primary outcome was treatment success at week 96. Treatment was considered a success if the participant was alive at week 96; had a plasma HIV-2 RNA of less than 50 copies per mL at week 96 (with a time window of week 92 to week 104); had a substantial CD4 cell count gain between inclusion and week 96; and had no serious morbidity episode between inclusion and week 96 (with a time window of week 92 to week 104). The CD4 cell count gain was considered substantial if the gain since baseline was 100 cells per µL or greater for patients with CD4 counts of 500 cells per µL or fewer at baseline, and any gain (ie, ≥1 cell per µL) for those who had more than 500 cells per µL at baseline. Serious morbidity was defined as any AIDS-defining event other than tuberculosis or any grade 3 or 4 cardiovascular, renal, or non-tuberculous bacterial event.

The main secondary outcomes were the occurrence of grade 3 or 4 adverse events of any type according to the Agence Nationale de Recherche sur le Sida (known as ANRS, Paris, France) grading table, changes in the CD4 cell count and plasma HIV-2 RNA, virological failure (ie, two consecutive plasma samples with HIV-2 RNA ≥50 copies per mL), HIV-2 drug resistance mutation, and permanent discontinuation of ART (appendix p 29).

Statistical analysis

A given ART regimen was considered highly effective if the rate of treatment success was higher than 70% at week 96 (expected level), and insufficiently effective if it was lower than 55% (unacceptable level; 56–69% was considered acceptable).

The primary analysis was in the intention-to-treat population and included all participants who were randomly assigned to treatment groups. Death and missing data at week 96 were considered treatment failure. In each ART regimen, the one-sided 95% CI of the proportion of monitored patients reaching the primary endpoint was calculated. The lower limit of the one-sided 95% CI had to be greater than 55% (ie, the unacceptable level) for the regimen to be considered sufficiently effective. A safety analysis was carried out at week 24. A data and safety monitoring board reviewed the week 24 analysis and had full access to the safety and efficacy data throughout the trial. SAS version 9.2 software was used to analyse the data.

Role of the funding source

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

Results

Between Jan 26, 2016, and June 29, 2017, 250 patients were screened, of whom 40 (16%) were excluded and 210 (84%) were randomly assigned to treatment groups. 71 (34%) participants were assigned to the triple NRTI group, 69 (33%) to the ritonavir-boosted lopinavir group, and 70 (33%) to the raltegravir group (figure 1). All participants were of sub-Saharan African origin. The trial ended on May 15, 2019, just before the COVID-19 pandemic, which made the movement of biological

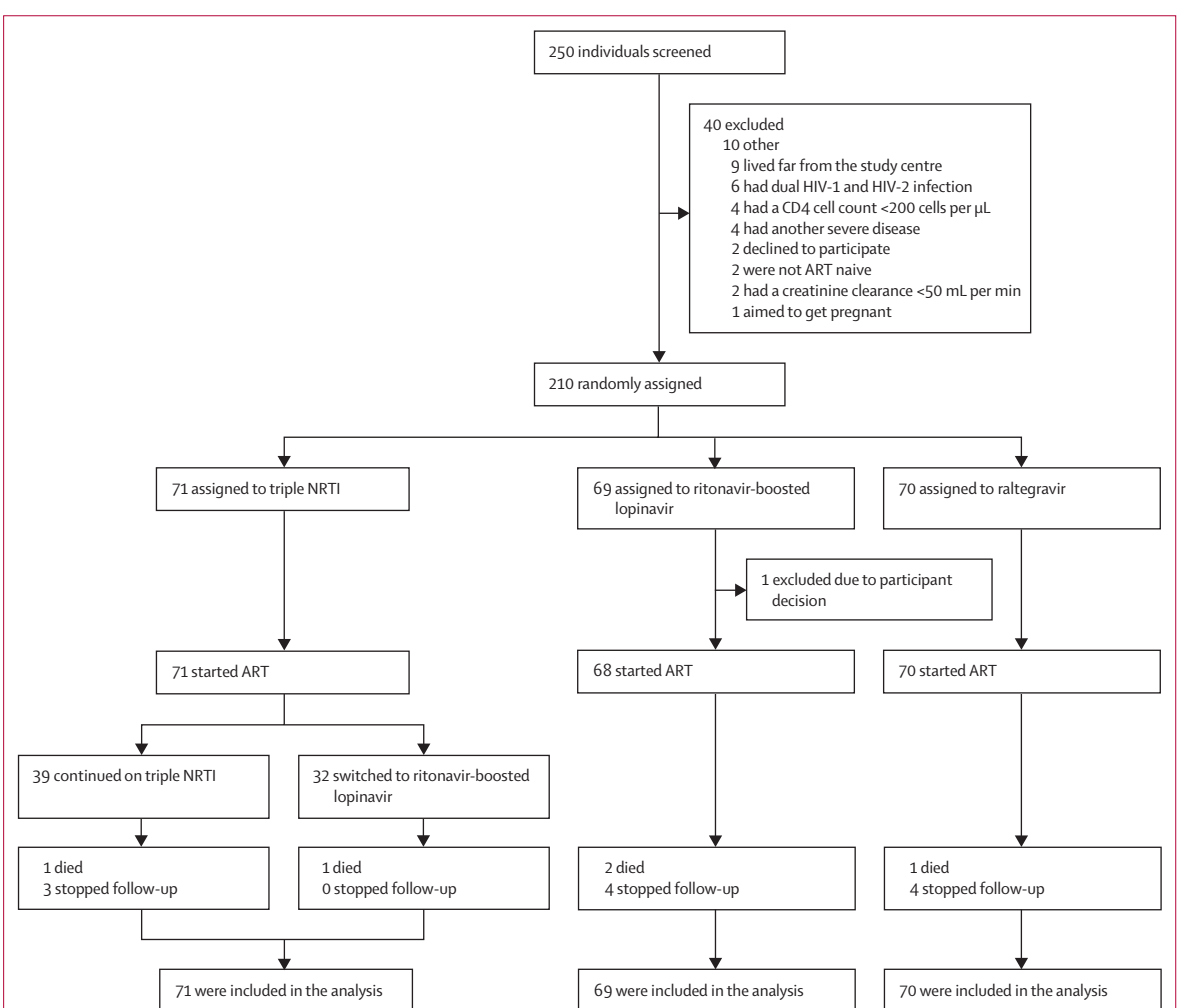

Figure 1: **Trial profile**

Among the 11 participants who permanently discontinued follow-up, two withdrew consent but agreed to be included in the analysis (one in the ritonavir-boosted lopinavir group and one in the raltegravir group), and nine were lost to follow-up (three in each group). ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor.

samples between countries and continents very difficult for 2 years. Therefore, it took 3 years in total to complete the virological database.

The median age was 51 years (IQR 47–57); 147 (70%) of 210 participants were female and 63 (30%) were male (table 1). 171 (81%) participants were at WHO clinical stage 1, 149 (71%) had a CD4 count of 500 cells per µL or more, and 161 (77%) had a plasma HIV-2 RNA of less than 50 copies per mL. In total, the participants were monitored for 368 person-years (median 96 weeks, IQR 96–97).

	Triple NRTI (n=71)	Ritonavir-boosted lopinavir (n=69)	Raltegravir (n=70)
Sex			
Male	19 (27%)	23 (33%)	21 (30%)
Female	52 (73%)	46 (67%)	49 (70%)
Age, years	52 (46–58)	52 (48–57)	50 (46–55)
WHO clinical stage			
1	59 (83%)	59 (86%)	53 (76%)
2	7 (10%)	5 (7%)	8 (11%)
3	5 (7%)	5 (7%)	9 (13%)
CD4 cell count			
Median (IQR) per µL	706 (496–946)	648 (479–811)	641 (452–865)
200–349 per µL	4 (6%)	5 (7%)	7 (10%)
350–499 per µL	14 (20%)	15 (22%)	15 (21%)
≥500 per µL	52 (74%)	49 (71%)	48 (69%)
Plasma HIV-2 RNA			
<50 copies per mL	61 (86%)	47 (68%)	53 (76%)
≥50 copies per mL	10 (14%)	22 (32%)	17 (24%)
Median (IQR) copies per mL	226 (143–698)	190 (96–1576)	401 (307–1871)
BMI, kg/m²	25·3 (23·0–29·8)	25·6 (22·7–30·1)	25·3 (21·8–28·2)
Positive plasma HBs antigen*	8 (11%)	0	7 (10%)
Positive plasma hepatitis C virus antibody*	3 (4%)	3 (5%)	2 (3%)
Haemoglobin, g/100 mL	12 (11–13)	13 (12–14)	12 (11–13)
Plasma alanine aminotransferase, IU	16 (11–22)	17 (14–23)	15 (11–20)
Creatinine clearance, mL per min†	98 (84–120)	99 (85–115)	97 (79–111)

Data are n (%) or median (IQR). IU=international unit. NRTI=nucleoside reverse transcriptase inhibitor. *Three participants had missing data, all in the ritonavir-boosted lopinavir group. †Clearance was estimated using the modification of diet in renal disease formula.

Table 1: **Baseline characteristics**

	Triple NRTI (n=71)	Ritonavir-boosted lopinavir (n=69)	Raltegravir (n=70)
Dead	2 (3%)	2 (3%)	1 (1%)
Missing data*	3 (4%)	5 (7%)	4 (6%)
Alive and all data available	66 (93%)	62 (90%)	65 (93%)
No episode of serious morbidity	62 (87%)	59 (86%)	64 (91%)
HIV-2 viral load of <50 copies per mL	64 (90%)	62 (90%)	65 (93%)
Substantial CD4 cell gain since inclusion†	39 (55%)	40 (58%)	42 (60%)
Combined primary endpoint			
Treatment failure	35 (49%)‡	30 (44%)	29 (41%)
Treatment success, n (%); one-sided 95% CI	36 (51%)‡; 41–60	39 (57%); 47–66	41 (59%); 49–68

Data are n (%) unless otherwise specified. NRTI=nucleoside reverse transcriptase inhibitor. *Missing data for at least one component of the primary endpoint. †Increase in CD4 count between baseline and week 96 of ≥100 cells per µL for patients who had <500 cells per µL at baseline or increase between baseline and week 96 of ≥1 cells per µL for patients who had ≥500 cells per µL at baseline. ‡The triple NRTI treatment was prematurely interrupted for safety reasons. Therefore, week 96 outcomes in this group do not reflect the efficacy of a triple nucleoside regimen.

Table 2: **Primary outcome**

The safety analysis at week 24 concluded that the study could continue (appendix p 5). Week 96 treatment success had a rate of 55% (n=116, one-sided 95% CI 50–61) overall: 51% (95% CI 41–60) in the triple NRTI group, 57% (47–66) in the ritonavir-boosted lopinavir group, and 59% (49–68) in the raltegravir group (table 2). The main reason for treatment failure was the absence of a substantial CD4 gain, which accounted for 27 (41%) of 66 in the triple NRTI group, 22 (35%) of 62 in the ritonavir-boosted lopinavir group, and 23 (35%) of 65 in the raltegravir group (Ns are for participants who were alive and had data available).

During follow-up, five (2%) of the 210 participants died, four (2%) had an AIDS-defining disease, and 37 (18%) had 41 non-AIDS-defining grade 3–4 disease (table 3). The median variation in bodyweight between baseline and week 96 was –1 kg (IQR –4 to 2) overall, –1 kg (IQR –4 to 2) in men and –2 kg (IQR –5 to 2) in women (appendix p 8).

Plasma HIV-2 RNA was measured in 198 (94%) of 210 participants at week 24, 197 (94%) of 210 at week 48, and 193 (92%) of 210 at week 96. Five (3%) of 198 individuals had plasma HIV-2 RNA of 50 copies per mL or more at week 24, eight (4%) of 197 at week 48, and two (1%) of 193 at week 96 (Ns are for participants who were alive and had data available; figure 2A). During follow-up, 17 (8%) of 210 participants had a plasma HIV-2 RNA of 50 copies per mL or more at least once, and seven (3%) at least twice (table 3; appendix p 6). Of the seven participants with at least two plasma HIV-2 RNA measurements of 50 copies per mL or more (ie, virological failure), six (86%) were in the triple NRTI group and one (14%) was in the ritonavir-boosted lopinavir group. All seven participants with virological failure had a plasma HIV-2 RNA concentration of 50 copies per mL or greater at baseline.

HIV-2 total DNA was measured in 188 (90%) of 210 participants at baseline, 172 (82%) at week 24, 181 (86%) at week 48, and 183 (87%) at week 96. HIV-2 total DNA levels were detectable (ie, ≥LOD) in 60 (32%) of 188 participants at baseline, 44 (26%) of 172 at week 24, 40 (22%) of 181 at week 48, and 44 (24%) of 183 at week 96; and quantifiable (ie, ≥LOQ) in three (2%) of 188 participants at baseline, two (1%) of 172 at week 24, 0 of 181 at week 48, and 1 (1%) of 183 at week 96. All three participants with a quantifiable HIV-2 total DNA at baseline had an HIV-2 total DNA below the LOQ at week 48 and week 96. Of the 185 patients with an HIV-2 total DNA below the LOQ at baseline, only one (1%) had a quantifiable HIV-2 total DNA during follow-up (75 copies per mL of whole blood at week 24 and 131 copies per mL at week 96). None of the seven patients

	Triple NRTI (n=71)	Ritonavir-boosted lopinavir (n=69)	Raltegravir (n=70)
Morbidity			
AIDS-defining morbidity	1 (1%)	2 (3%)	1 (1%)
Other grade 3–4 morbidity			
Invasive bacterial diseases	1 (1%)	3 (4%)	0
Serious cardiovascular disorders	2 (3%)	0	1 (1%)
Serious renal disorders	0	1 (1%)	0
Malignancies	0	0	2 (3%)
Serious digestive disorders	6 (9%)	4 (6%)	0
Serious haematological disorders	5 (7%)	1 (1%)	5 (7%)
Death of unexplained cause	2 (3%)	1 (1%)	0
Any other grade 3–4 morbidity	3 (4%)	1 (1%)	3 (4%)
Plasma HIV-2 RNA			
≥10 copies per mL at least once	22 (31%)	21 (30%)	8 (11%)
≥50 copies per mL at least once	11 (16%)	4 (6%)	2 (3%)
Virological failure	6 (9%)	1 (1%)	0
ART modifications			
Switch to another regimen	32 (45%)	0	0
Permanent ART discontinuation	5 (7%)	7 (10%)	6 (9%)

ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. Virological failure was defined as two consecutive measurements of plasma HIV-2 RNA >50 copies per mL. Three deaths were of unknown cause; the remaining two deaths were associated with severe sepsis (n=1) and breast cancer (n=1). AIDS-defining morbidity was extra pulmonary tuberculosis (n=2) and fungal oesophagitis (n=2). Invasive bacterial diseases identified were bacterial pneumonia (n=2), prostatitis (n=1), and severe sepsis (n=1). Serious cardiovascular disorders identified were peripheral arterial occlusive disease (n=1) and stroke (n=2). Malignancies identified were breast cancer (n=2). Serious digestive disorders identified were vomiting, diarrhoea, or abdominal pain (n=7), pancreatitis (n=1), intestinal occlusion (n=1), and gastric perforation (n=1). Serious haematological disorders identified were neutropenia (n=7), anaemia (n=3), and anaemia and neutropenia (n=1). Other grade 3–4 morbidity identified were hypocalcaemia (n=2), hypercalcaemia (n=1), diabetes (n=1), neuropsychiatric disorders (n=1), elevation of alkaline phosphatases (n=1), and dyspnoea (n=1). Reasons for switching to another regimen were virological failure (n=2), adverse events (n=9), and due to a decision by the treating physician following the advice of the Data Safety Monitoring Board (n=21).

Table 3: **Secondary outcomes**

with virological failure had quantifiable HIV-2 DNA at baseline or during follow-up.

Drug resistance tests were done for five of the seven participants with virological failure (four in the triple NRTI group and one in the ritonavir-boosted lopinavir group). Two of these participants had viruses with several NRTI resistance mutations (Lys65Arg-Thr69Ser-Val111Ile-Tyr115Phe-Met184Val and Lys65Arg-Thr69Ser-Met184Val) detected at week 96. The remaining three had no resistance mutations.

The median variation in CD4 count between baseline and week 96 was 105 cells per µL (IQR –31 to 231) overall, 142 cells per µL (56 to 230) in participants with a baseline CD4 count less than 500 cells per µL, and 88 cells per µL (–79 to 231) in those with a baseline CD4 count of 500 cells per µL or greater (table 1, figure 2B).

The Data Safety Monitoring Board reviewed the results of the week 24 safety analysis on April 6, 2018, and recommended stopping the triple NRTI group for safety reasons. This recommendation was based on the following findings at the time of the data review. First, six (9%) of the 71 participants in the triple NRTI group had virological failure (including five who had a quantifiable viral load at baseline), while no virological failure was observed in the other groups. Only one of these six participants were confirmed to be non-compliant. Second, nine (13%) participants in the triple NRTI group had discontinued treatment for adverse effects (five for digestive adverse effects and four for anaemia) versus three (2%) of 139 in the other two groups. In the triple NRTI group, participants who discontinued for adverse effects did not overlap with those who had virological failure.

One participant in the ritonavir-boosted lopinavir group never started ART. During the entire follow-up period, 50 (24%) of the 210 participants discontinued the ART regimen assigned at randomisation, including 32 (15%) who switched to another ART regimen and 18 (9%) who discontinued ART permanently.

Participants who switched to another regimen were all in the triple NRTI group. Reasons for switching were virological failure (n=2), adverse events (n=9), or recommendation by the Data Safety Monitoring Board (n=21). All of these participants switched to ritonavir-boosted lopinavir. One individual died 2·4 months after switching.

Among the 18 participants who discontinued ART permanently, 11 discontinued trial follow-up (three in the triple NRTI group, four in the ritonavir-boosted lopinavir group, and four in the raltegravir group), three completed follow-up but indicated they did not wish to continue ART (one in the triple NRTI group, one in the ritonavir-boosted lopinavir group, and one in the raltegravir group), and four died while they were still receiving the ART regimen assigned at randomisation (one in the triple NRTI group, two in the ritonavir-boosted lopinavir group, and one in the raltegravir group).

Discussion

HIV-2 infection is much less common than HIV-1, is mainly concentrated in west Africa, and is less severe and less replicative than HIV-1.[5,7,24] The rarity of HIV-2 means that certain features of the virus, particularly those concerning its sensitivity to antiretroviral drugs, are less well known, and that the organisation of randomised trials to identify the most effective drug combinations is more difficult than for HIV-1. As HIV-2 is less replicable than HIV-1, viral load control—the standard success criterion used to monitor the efficacy

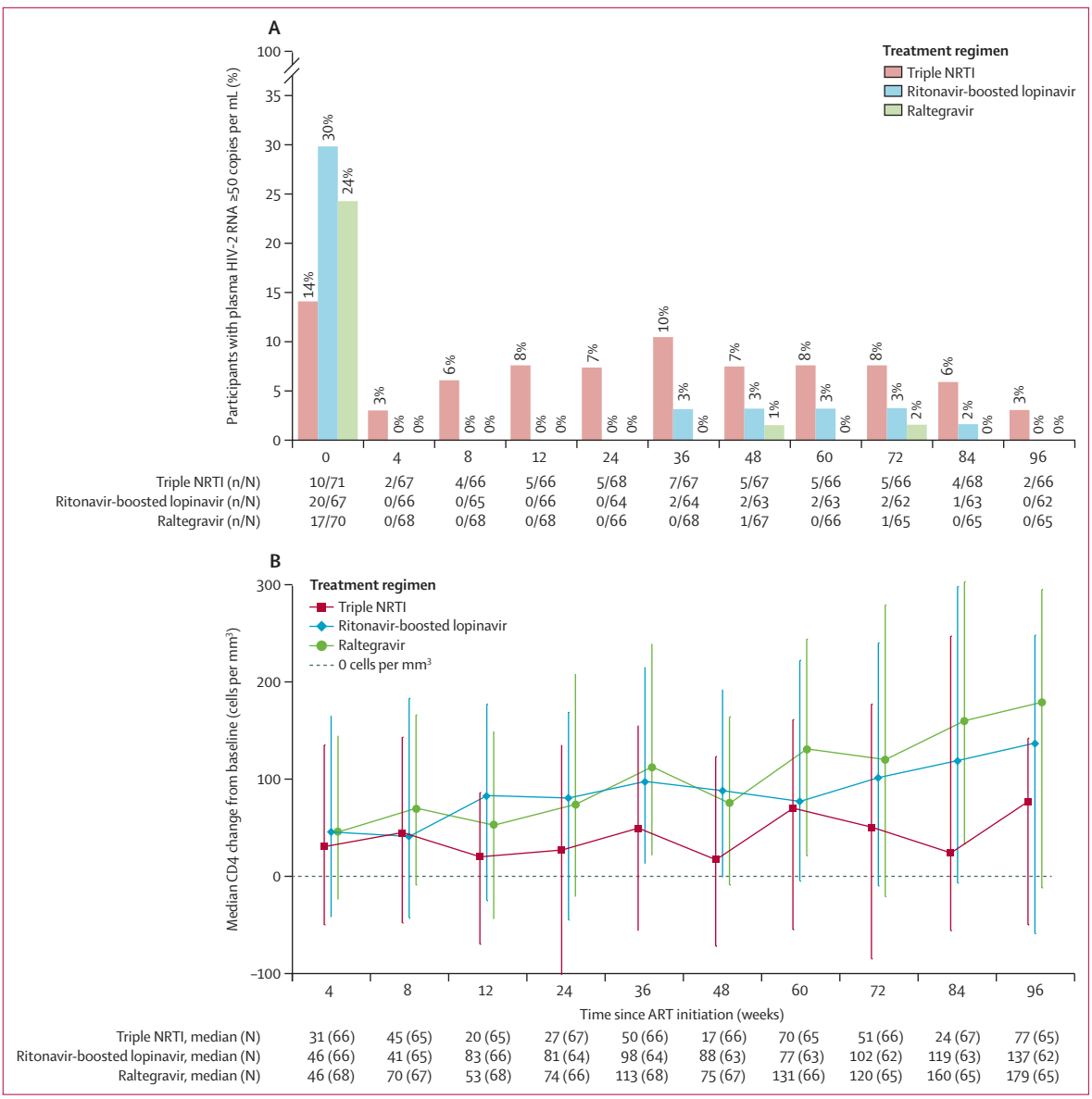

Figure 2: **Plasma HIV-2 RNA and CD4 cell count variation over time, according to treatment group**
(A) Plasma HIV-2 RNA over time, according to treatment group. (B) CD4 cell count variation over time, according to treatment group. Error bars are IQRs. ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor.

of ART in HIV-1 infection—cannot be used for monitoring the efficacy of ART in HIV-2 infection.[25]

We did a pilot randomised trial to evaluate three ART regimens in west African adults with HIV-2 who were treatment naive. The aim was not to compare the three regimens with each other, but to assess each of them for future phase 3 studies, and to do so in parallel by ensuring that all three groups broadly had the same baseline characteristics to facilitate specification of the parameters for a possible future trial.

The triple NRTI group was discontinued. The results from this group are sufficient to discount it for routine use. This group was clearly the least effective virologically and the least well tolerated.[26,27] The ritonavir-boosted lopinavir and raltegravir groups did not reach the success criterion we had set a priori due to the immunological component of the composite criterion, which was difficult to set in advance. However, the treatments were well tolerated in both groups, virological failures and morbidity and mortality were rare, and CD4 cell count gains were good. These results suggest that both regimens are acceptable for future randomised trials, which should also consider using more conservative criteria to define treatment success.

Since future phase 3 trials comparing these two regimens would require hundreds of participants, who

would probably be difficult to recruit, various observations can be made in the meantime, based on our results and data available elsewhere.

Boosted protease inhibitor regimens have long been the preferred treatment option in HIV-2 infection, with ritonavir-boosted lopinavir being the most widely used and best described protease inhibitor in cohort studies.[7,16]

Since 2018, WHO has recommended a dolutegravir-based regimen as a first-line option for individuals with HIV-2.[28] This recommendation, based on virological data and a parallel with recommendations made for HIV-1 treatment, has been supported by two non-comparative trials[10,13] in people with HIV-2 in France and Senegal (one with raltegravir and the other with elvitegravir). These two pilot studies showed good efficacy and tolerability, with rates similar to those reported for the present study.[10,13] Our data suggest a trend towards better viral control and higher CD4 cell count gains in the raltegravir group, which does not prove its superiority but tends to support the WHO recommendation. Moderate weight gain was observed in the raltegravir group, whereas weight loss was more common in the other two groups, which is consistent with a trend towards better immunological and virological efficacy. In both groups, an absence of evidence for being overweight was observed, which is reassuring as this is one of the effects currently being monitored in African people taking second-generation INSTIs, especially in women.[29]

Our study has several limitations. First, this was a pilot, non-comparative study, in which the number of participants was small and the success rate was lower than expected even in the treatment group considered the reference, which resulted in the trial being underpowered. The data collected are useful for posing hypotheses for future studies, but do not provide strong evidence for the comparative effectiveness of the treatments studied. Second, we used a composite endpoint because using mortality as the primary endpoint was not feasible. In HIV-1 trials, clinical, immunological, and virological failure or success are routinely used as surrogate endpoints. Our definitions of immunological and virological success were questionable; a CD4 gain of at least 1 cell per µL reflects the absence of immunological worsening more than immunological success. An unquantifiable viral load on treatment does not have the same meaning for people whose pre-ART viral load was quantifiable as it does for those whose viral load was already unquantifiable before they started ART. These two questions of defining immunological and virological success highlight the difficulty in defining the best surrogate endpoints to be used in HIV-2 trials. Third, the follow-up was limited to 96 weeks and weight gain on a raltegravir-based regimen could have been greater over a longer term. Fourth, the study was unmasked. Knowledge of the treatment randomisation could have influenced clinician and participant behaviours in the ongoing management or the ascertainment of efficacy and safety outcomes. Fifth, we excluded people with CD4 counts of less than 200 cells per µL because the treatment options included a triple nucleoside regimen. Had we included more participants with advanced-stage disease, the proportion of individuals with a quantifiable viral load would have been higher and, consequently, virological efficacy would have been easier to measure. However, at a time when ART is recommended for all individuals regardless of their CD4 cell count, on the basis of evidence coming from HIV-1 studies,[30,31] it is particularly important to discuss the value of early ART in individuals with HIV-2. Treating people with HIV-2 at early stages in this study provided original data highlighting how the issue of HIV-2 treatment requires a specific approach compared with HIV-1. HIV-2 has a lower replication rate and progresses more slowly than HIV-1. However, our data show that people with HIV-2 who still have high CD4 cell counts when beginning treatment undergo an increase in their CD4 cell count while having treatment, which suggests a benefit in terms of immune defence in these participants. Therefore, the question of when to treat an individual, which no longer arises for HIV-1, might remain relevant for HIV-2. Addressing this question would require identification of the threshold (if any) above which the benefit of treating would be equal to or smaller than the risk.

In conclusion, triple nucleoside regimens should not be used in adults with HIV-2, while raltegravir-based and boosted lopinavir-based regimens could be compared in future phase 3 trials. The results of this pilot trial suggest a trend towards better virological and immunological efficacy for the raltegravir-based regimen. Since most individuals with HIV-2 are located in west Africa, weight gain and metabolic complications should be carefully studied in these individuals who receive INSTIs.[32]

Contributors

XA, SPE, DKE, ChC, CoC, and FB-V designed the study. EuM, EpM, ZD, JZ, AM, NFNG, DH, FD, MS, ID, AP, and YJD recruited and monitored the participants. AT-G, CoC, GC, BT, JLC, and SK coordinated the data management and study monitoring. A-SO, ChC, T-d'AT, GB, CTK, and FB-V carried out the virological tests. CoC, DKE and XA analysed the data. All authors reviewed the final report. XA, SPE, DKE, CoC, ChC, and FB-V accessed and verified the data and drafted the manuscript. All authors critically reviewed the manuscript and read and approved the final version for submission and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data and codes will be made available from the corresponding author upon reasonable request.

Acknowledgments

FIT-2 ANRS 12294 was funded by the French Agency for Research on AIDS and Viral Hepatitis (ANRS MIE), an agency of the Institut National de la Sante et de la Recherche Medicale (Inserm, Paris, France). We thank everyone who agreed to participate in the study, the ANRS MIE team, the patient organisations for their advice and support, the staff of the centres that took part in the study, and the members of

the FIT-2 study group. Raltegravir was donated by Merck Sharp & Dohme and other drugs were provided by the national AIDS programme in each country.

References

1 Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. *Clin Infect Dis* 2011; **52:** 780–87.

2 Kapoor AK, Padival S. HIV-2. 2022. https://www.ncbi.nlm.nih.gov/books/NBK572083/ (accessed Feb 22, 2023).

3 Wittkop L, Arsandaux J, Trevino A, et al. CD4 cell count response to first-line combination ART in HIV-2+ patients compared with HIV-1+ patients: a multinational, multicohort European study. *J Antimicrob Chemother* 2017; **72:** 2869–78.

4 Whittle H, Morris J, Todd J, et al. HIV-2-infected patients survive longer than HIV-1-infected patients. *AIDS* 1994; **8:** 1617–20.

5 Ekouévi DK, Avettand-Fènoël V, Tchounga BK, et al. Plasma HIV-2 RNA according to CD4 count strata among HIV-2-infected adults in the IeDEA West Africa Collaboration. *PLoS One* 2015; **10:** e0129886.

6 Popper SJ, Sarr AD, Guèye-Ndiaye A, Mboup S, Essex ME, Kanki PJ. Low plasma human immunodeficiency virus type 2 viral load is independent of proviral load: low virus production in vivo. *J Virol* 2000; **74:** 1554–57.

7 Ekouevi DK, Tchounga BK, Coffie PA, et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. *BMC Infect Dis* 2014; **14:** 461.

8 Ren J, Bird LE, Chamberlain PP, Stewart-Jones GB, Stuart DI, Stammers DK. Structure of HIV-2 reverse transcriptase at 2.35-A resolution and the mechanism of resistance to non-nucleoside inhibitors. *Proc Natl Acad Sci USA* 2002; **99:** 14410–15.

9 Witvrouw M, Pannecouque C, Switzer WM, Folks TM, De Clercq E, Heneine W. Susceptibility of HIV-2, SIV and SHIV to various anti-HIV-1 compounds: implications for treatment and postexposure prophylaxis. *Antivir Ther* 2004; **9:** 57–65.

10 Gottlieb GS, Smith RA, Dia Badiane NM, et al. HIV-2 integrase variation in integrase inhibitor-naïve adults in Senegal, west Africa. *PLoS One* 2011; **6:** e22204.

11 Descamps D, Peytavin G, Visseaux B, et al. Dolutegravir in HIV-2-infected patients with resistant virus to first-line integrase inhibitors from the French named patient program. *Clin Infect Dis* 2015; **60:** 1521–27.

12 Treviño A, Cabezas T, Lozano AB, et al. Dolutegravir for the treatment of HIV-2 infection. *J Clin Virol* 2015; **64:** 12–15.

13 Matheron S, Descamps D, Gallien S, et al. First-line raltegravir/emtricitabine/tenofovir combination in human immunodeficiency virus type 2 (HIV-2) infection: a phase 2, noncomparative trial (ANRS 159 HIV-2). *Clin Infect Dis* 2018; **67:** 1161–67.

14 Ba S, Raugi DN, Smith RA, et al. A trial of a single-tablet regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate for the initial treatment of human immunodeficiency virus type 2 infection in a resource-limited setting: 48-week results from Senegal, west Africa. *Clin Infect Dis* 2018; **67:** 1588–94.

15 WHO. Global update on HIV treatment 2013: results, impact and opportunities. WHO report in partnership with UNICEF and UNAIDS. 2013. https://www.unaids.org/en/resources/documents/2013/20130630_treatment_report (accessed Oct 17, 2023).

16 Benard A, van Sighem A, Taieb A, et al. Immunovirological response to triple nucleotide reverse-transcriptase inhibitors and ritonavir-boosted protease inhibitors in treatment-naive HIV-2-infected patients: the ACHIEV2E Collaboration Study Group. *Clin Infect Dis* 2011; **52:** 1257–66.

17 Gilleece Y, Chadwick DR, Breuer J, et al. British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med* 2010; **11:** 611–19.

18 Gottlieb GS, Eholié S-P, Nkengasong JN, et al. A call for randomized controlled trials of antiretroviral therapy for HIV-2 infection in west Africa. *AIDS* 2008; **22:** 2069–72.

19 Avettand-Fenoel V, Damond F, Gueudin M, et al. New sensitive one-step real-time duplex PCR method for group A and B HIV-2 RNA load. *J Clin Microbiol* 2014; **52:** 3017–22.

20 Laurendeau I, Bahuau M, Vodovar N, et al. TaqMan PCR-based gene dosage assay for predictive testing in individuals from a cancer family with INK4 locus haploinsufficiency. *Clin Chem* 1999; **45:** 982–86.

21 Dehee A, Asselot C, Piolot T, et al. Quantification of Epstein-Barr virus load in peripheral blood of human immunodeficiency virus-infected patients using real-time PCR. *J Med Virol* 2001; **65:** 543–52.

22 Bertine M, Gueudin M, Mélard A, et al. New highly sensitive real-time PCR assay for HIV-2 Group A and Group B DNA quantification. *J Clin Microbiol* 2017; **55:** 2850–57.

23 Charpentier C, Camacho R, Ruelle J, et al. HIV-2EU: supporting standardized HIV-2 drug resistance interpretation in Europe. *Clin Infect Dis* 2013; **56:** 1654–58.

24 Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. *Clin Infect Dis* 2011; **52:** 780–87.

25 Gottlieb GS, Eholié S-P, Nkengasong JN, et al. A call for randomized controlled trials of antiretroviral therapy for HIV-2 infection in west Africa. *AIDS* 2008; **22:** 2069–74.

26 Benard A, van Sighem A, Taieb A, et al. Immunovirological response to triple nucleotide reverse-transcriptase inhibitors and ritonavir-boosted protease inhibitors in treatment-naive HIV-2-infected patients: the ACHIEV2E Collaboration Study Group. *Clin Infect Dis* 2011; **52:** 1257–66.

27 Ouattara E, Danel C, Moh R, et al. Early upper digestive tract side effects of zidovudine with tenofovir plus emtricitabine in west African adults with high CD4 counts. *J Int AIDS Soc* 2013; **16:** 18059.

28 WHO. WHO recommends dolutegravir as preferred HIV treatment option in all populations. 2019. https://www.who.int/news/item/22-07-2019-who-recommends-dolutegravir-as-preferred-hiv-treatment-option-in-all-populations (accessed July 25, 2023).

29 NAMSAL ANRS 12313 Study Group, Kouanfack C, Mpoudi-Etame M, et al. Dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1. *N Engl J Med* 2019; **381:** 816–26.

30 TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.

31 Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373:** 795–807.

32 Brennan AT, Nattey C, Kileel EM, et al. Change in body weight and risk of hypertension after switching from efavirenz to dolutegravir in adults living with HIV: evidence from routine care in Johannesburg, South Africa. *EClinicalMedicine* 2023; **57:** 101836.