AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000002320

UPTAKE AND EFFECTIVENESS OF TWO-DRUG COMPARED TO THREE-DRUG ANTIRETROVIRAL REGIMENS AMONG HIV-POSITIVE INDIVIDUALS IN EUROPE

Running title: ***Uptake & Effectiveness of 2DR vs 3DR***

Bastian NEESGAARD[1], Annegret PELCHEN-MATTHEWS[2], Lene RYOM[1], Eric FLORENCE[3], Lars PETERS[1], Ashley ROEN[2], Veronika SVEDHEM[4], Amanda CLARKE[5], Thomas BENFIELD[6], Viktar MITSURA[7], Santiago MORENO[8], Marek BENIOWSKI[9], Josip BEGOVAC[10], Raimonda MATULIONYTE[11], Tatyana TROFIMOVA[12], Daniel ELBIRT[13], Mariana KUNDRO[14], Vincenzo VULLO[15], Georg BEHRENS[16], Therese STAUB[17], Leigh RAGONE[18], Vani VANNAPPAGARI[18], Jens LUNDGREN[1] and Amanda MOCROFT[2] on behalf of the EuroSIDA study

1 CHIP, University of Copenhagen, Denmark; **2** University College London, UK; **3** Institute of Tropical Medicine, Antwerp, Belgium; **4** Department of Infectious Diseases, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; **5** Royal Sussex County Hospital, Brighton, UK; **6** Hvidovre Hospital, University of Copenhagen, Denmark; **7** Gomel State Medical University, Belarus; **8** Hospital Ramon y Cajal, Madrid, Spain; **9** Szpital Specjalistyczny, Chorzów Poland, **10** University Hospital of Infectious Diseases, Zagreb, Croatia; **11** Vilnius University, Faculty of Medicine; Vilnius University Hospital Santaros Klinikos; **12** Novgorod Centre for AIDS Prevention and Control, Russia; **13** Kaplan Medical

Center, Rehovot, Israel; 14 Hospital JM Ramos Mejia, Buenos Aires, Argentina; **15** Sapienza University of Rome, Italy; **16** Medizinische Hochschule Hannover, Germany; **17** Centre Hospitalier de Luxembourg; **18** ViiV Healthcare, RTP, North Carolina, USA.

Conflicts of Interest and Source of Funding

EuroSIDA was supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n° 260694. Current support includes unrestricted grants by ViiV Healthcare LLC, GlaxoSmithKline R&D Limited, Janssen Scientific Affairs, Janssen R&D, Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp, Gilead Sciences. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 148522). The study is also supported by a grant [grant number DNRF126] from the Danish National Research Foundation and by the International Cohort Consortium of Infectious Disease (RESPOND). This specific analysis was supported by ViiV Healthcare

The corresponding author declares no conflict of interest.

Corresponding author:

Bastian Neesgaard, MD

CHIP, Department of Infectious Diseases, Section 2100

Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

E-mail: Bastian.neesgaard@regionh.dk

Tel: +45 35 45 57 70; Fax: +45 35 45 57 58

Abstract:

Objective*:* To assess the use of two-drug antiretroviral regimens (2DR) and virologic and immunologic outcomes compared to three-drug regimens (3DR) in the EuroSIDA cohort.

Design: Multicentre, prospective cohort study.

Methods: Logistic regression was used to analyse the uptake and outcomes among HIV-positive individuals who started or switched to a 2DR compared to those on a 3DR. Virologic outcomes were assessed on-treatment as the proportion of individuals with controlled viral load (VL, <400 copies/mL), or with a composite modified FDA snapshot endpoint (mFDA), with mFDA success defined as controlled VL at 6- or 12-months for individuals with a known VL, no regimen changes, AIDS or death. Immunologic response was defined as a 100 cells/μL or a 25% increase in CD4 counts from baseline.

Results: Between 1/7/2010-31/12/2016, 423 individuals started or switched to a 2DR (8 antiretroviral-naïve) and 4347 started a 3DR (566 naïve). Individuals on 2DR tended to have suppressed VL, higher CD4 cell counts and more comorbidities at baseline compared to those on 3DR. There were no differences in the proportions of individuals who obtained on-treatment or mFDA success, and no significant differences in the adjusted odds ratios for mFDA success or immunologic responses between the 2DR and 3DR groups at 6- or 12-months.

Conclusion: In routine clinical practice, 2DR were largely used for virologically suppressed individuals with higher cumulative exposure to ARVs and comorbidities. Virologic and immunologic outcomes were similar among those on 2DR or 3DR, although confounding by indication cannot be fully excluded due to the observational nature of the study.

Key-words: HIV**,** Two-drug regimens, simplification, cART, NRTI-sparing regimens, dual therapy

Introduction:

Combination antiretroviral treatment (cART), given as a three-drug regimen (3DR) consisting of two nucleot(s)ide reverse transcriptase inhibitors (NRTIs) together with a non-nucleotide reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or integrase inhibitor (INSTI) has been the standard treatment for HIV for more than two decades.[1, 2] Although 3DRs are effective in maintaining virological suppression, lifelong treatment is needed, with increased concerns for long term toxicities and drug-drug interaction,[3-5] especially as the population of people living with HIV (PLWHIV) ages.[6] One approach to address these concerns is treatment-simplification to NRTI-sparing two-drug regimens (2DR), consisting of exactly two active drugs, which has become feasible with the introduction of potent PIs and INSTIs.

Randomized clinical trials (RCTs) are necessary to evaluate drug efficacy, and studies on 2DR approaches have yielded promising results. For example, studies of 2DR therapy with boosted PIs in combination with NRTIs have overall shown good ability to suppress viral replication,[7-9] and with the advent of INSTIs with high genetic barriers, potent antiretroviral (ARV) activity and low numbers of reported adverse effects,[10-12] the interest in diverse combinations of INSTI- and PI-based 2DRs has increased.[13-19] However, RCTs are intrinsically limited by modest sample sizes and inclusion of highly selected groups of individuals. Findings from RCTs are thus not necessarily generalizable to the majority of PLWHIV seen in routine clinical care, as persons with co-existing comorbidities, low CD4 cell counts or high-level HIV viremia are often underrepresented. Results from RCTs therefore need to be complemented by investigations in larger and more heterogeneous observational studies.

As 2DR are now also included as class-sparing strategies under certain circumstances in European and North American guidelines,[1, 2] 2DR use in clinical practice will presumably

increase in the coming years. However, there have been only a few studies assessing the performance of 2DR in real-life settings, based on relatively small cohorts and/or selected patient groups with limited heterogeneity.[20-23] Here we analysed the uptake of 2DRs, factors associated with starting or switching to a 2DR in the European based EuroSIDA cohort, and virologic and immunologic outcomes of using 2DRs compared 3DRs in this large, heterogeneous, population of PLWHIV seen in routine clinical care.

Methods:

Study design – the EuroSIDA cohort:

This investigation was conducted as part of the EuroSIDA study, a prospective observational cohort study that currently holds data on more than 23,000 PLWHIV in 35 European countries, Israel and Argentina. The main objective of the study is to describe the long-term clinical prognosis of PLWHIV in Europe (https://www.chip.dk/Studies/EuroSIDA). All individuals gave informed consent at enrolment into the EuroSIDA study.

Inclusion and exclusion criteria

Individuals who started or switched to an ARV regimen consisting of two drugs, one of which was darunavir (DRV), lopinavir (LPV), raltegravir (RAL), dolutegravir (DTG), rilpivirine (RPV) or etravirine (ETR), were included during prospective follow-up between 1st July 2010 (the date when use of 2DR became increasingly common) and 31st December 2016, with the date of starting the regimen of interest defined as baseline. Individuals were only included for their first eligible 2DR, or for those who were never on a 2DR during follow-up, for their first eligible 3DR. To ensure comparability, the 3DR group consisted of individuals treated with two NRTIs together with DRV, LPV, RAL, DTG, RPV or ETR as the third ARV during the same study period. If ritonavir or cobicistat were used as boosting agents, they were not considered as one of the ARV drugs in the 2DR or 3DR. Individuals

were aged ≥16 years at baseline and had a viral load (VL) and CD4 count measured in the 12 months prior to baseline (see Supplementary Fig. 1).

Definition of co-morbidities and clinical events:

Cardiovascular disease (CVD) and D:A:D 5-year CVD risk were defined and calculated as in Friis-Moller et al.[24] Hypertension and dyslipidaemia followed standard definitions; systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or on antihypertensive drugs, and total cholesterol ≥6.2 mmol/l, high density lipoprotein cholesterol ≤0.9 mmol/l or triglycerides >2.3 mmol/l respectively. For diabetes we followed a clinical definition of diabetes and/or use of antidiabetic drugs. We calculated estimated glomerular filtration rates (eGFR) with the CKD-EPI creatinine equation, while chronic kidney disease (CKD) and D:A:D 5-year CKD risk were defined and calculated as in Mocroft et al.[25] End-stage renal disease (ESRD) was defined as a clinical diagnosis of ESRD, or confirmed eGFR ≤15 mL/min. (≥3 months apart). Liver-related events (LRE) included a composite diagnosis of ascites, hepatic encephalopathy grade 3 or 4, hepatorenal syndrome, oesophageal variceal bleeding, end-stage liver disease without specifications and hepatocellular carcinoma.

New clinical events, calculated as incidence per 1000 person years of follow up (PYFU), were assessed for all persons. Events included death, any new AIDS defining event (malignant or non-malignant), non-AIDS defining malignancy, CVD (myocardial infarction, stroke or invasive cardiovascular procedure), CKD or liver-related events.

Statistical analysis:

All analyses were performed using SAS (Statistical Analysis Software, Cary, NC, US) version 9.4. P-values of <0.05 were considered statistically significant and we used 95% confidence intervals (CIs).

Descriptive statistics were summarized as frequencies and proportions with χ^2 P-values for categorical variables. For continuous variables, data were presented as medians and interquartile ranges (IQR), with P-values from the Wilcoxon-Mann-Whitney non-parametric test.

Outcomes were assessed using logistic regression. Factors considered for univariate analyses were age, gender, ethnic group, region of Europe, mode of infection, time since HIV diagnosis, prior AIDS defining disease, baseline CD4 count, nadir CD4 count, VL, prior ARV exposure, number of ARVs previously exposed to, time on ARVs, prior exposure to NRTIs, NNRTIs, boosted PIs, INSTIs, or other ARVs, co-morbidities and risk score. All multivariable logistic regression modelling shown used forward selection in order to find variables which contribute significantly to the model ($p < 0.1$), with additional key variables forced in.

Immunologic and virologic outcomes were assessed at 6- or 12-months after baseline, among all persons with the potential for 6- or 12-months follow-up. The VL and CD4 count immediately before the 6- or 12-months point was used for analysis or, where this was not available, the first count after, using at most a 16-week period either side of 6- or 12-months.

Virologic control was defined as a VL of <400 HIV RNA copies(cp)/mL. A modified composite FDA snapshot endpoint (mFDA) was used to determine virologic responses at 6- or 12-months ± 16 weeks. Individuals with <400 HIV RNA cp/mL in this time window were classed as mFDA success, while individuals with at least one of: VL ≥400 cp/mL, unknown VL in the time window of interest, regimen changes (switched or stopped any of the drugs in the regimen before the end of the period), a new AIDS-defining event or death were considered mFDA failures. Immunologic outcomes were evaluated as the proportion of individuals with a 100 cells/μL or a 25% increase in CD4 count from baseline.

In on-treatment analyses we estimated the proportion of individuals on a 2DR or 3DR who achieved a VL < 400 cp/mL at 6- or 12-months ± 16 weeks, among individuals with a known VL and no regimen changes.

In order to cover VL assays used in the time period and throughout the region a cut-off <400 cp/mL has been applied for the main analysis, while also performing sensitivity analyses defining mFDA and on-treatment success as <50 cp/mL at 6- or 12- months ± 16 weeks.

Outcomes were determined for the study participants overall or stratified into three pre-specified groups, treatment-naïve individuals, treatment-experienced individuals with virologic failure (≥400 cp/mL) on the previous regimen, and treatment-experienced individuals with virologic control (<400 cp/mL) at baseline.

Results:

Baseline demographic and clinical characteristics

Of the 23071 individuals included in the EuroSIDA study, 4770 (20.7%) were eligible for inclusion into the analysis (Supplementary Fig. 1a), of whom 423 (8.9%) were treated with a 2DR and 4347 (91.1%) with a 3DR.

Two-hundred-and-eighty (66.2%) of the 2DR included a boosted PI and 334 (79.0%) an INSTI (note 191 (45.2%) individuals were on a PI+INSTI 2DR). The four most common 2DR were DRV + RAL (n=153, 36.2%), DRV/r + 3TC (n=77, 18.2%), RAL + ETR (n=66, 15.6%) and DTG + 3TC (n=39, 9.2%; see supplementary Fig. 1b). The most common third ARV drugs in the 3DR group were DRV/r (n=1117, 25.7%) followed by LPV/r (n=887, 20.4%), and DTG (n=774, 17.8% (Supplementary Fig. 1c). Among the 3DR group the most common NRTI backbone used was tenofovir disoproxil fumarate + emtricitabine (n=2284, 52.5%) followed by abacavir + 3TC (n=1395, 32.1%). Baseline was significantly later for

those treated with a 2DR (median 31/07/14 (IQR 26/10/12 - 26/10/15)) compared to a 3DR (median 01/10/13 (IQR 22/03/12 - 30/03/15); p <0.0001).

Table 1 shows the baseline demographic and clinical characteristics of persons included. Individuals receiving a 2DR were older than those starting 3DR (median age 52.1 years (IQR 46.2 - 57.6) versus 46.4 years, (IQR 37.8 - 53.1). The majority in both groups were males, with men who have sex with men being the most common route of HIV transmission. A higher proportion of those receiving a 2DR had a CD4 count >500 cells/μL and VL <400 cp/mL compared to those receiving a 3DR. Individuals in the 2DR group were more extensively pre-treated prior to baseline. Apart from current smoking status (39% vs. 46%), persons in the 2DR group had a higher prevalence of risk factors and comorbidities including diabetes, CVD, LRE and CKD.

Factors associated with treatment with a 2DR versus 3DR

Table 2 shows the univariate and multivariable odds ratios for starting or switching to treatment with a 2DR versus 3DR. After adjustment, individuals from Southern Europe were more likely to receive a 2DR than those from Northern or Eastern Europe. Persons on a 2DR were more likely to have previously been treated with a boosted PI or INSTI. A high or very high D:A:D 5-year CVD risk score and ESRD were also associated with higher adjusted odds of receiving a 2DR. After adjustment for the other factors, prior exposure to NRTIs or NNRTIs was not significantly associated with treatment with a 2DR.

Virologic and immunologic outcomes of 2DR versus 3DR

VL at follow-up was available for 85.5% and 85.4% of the participants at 6 months, and for 79.9% and 80.7% at 12 months for individuals in the 2DR and 3DR group, respectively. The crude proportion of individuals with controlled viral load in the on-treatment analysis was marginally greater for the 2DR group versus the 3DR group at 6 months; 98.3% (95%: 96.1-

99.5) vs. 94.4% (93.5-95.2), but similar at 12 months; 98.2% (95.4-99.5) vs. 95.6% (94.5-94.9) (Fig. 1) and consistent in a sensitivity analysis with on-treatment success defined as <50 cp/mL (data not shown).

The overall proportion of mFDA success (2DR and 3DR groups combined), was 3204/4581 (69.9%) and 2521/4230 (59.6%) at 6- and 12-months, respectively. Of the 423 individuals who initiated a 2DR, 398 and 344 had follow-up data available at 6- and 12-months respectively. Of these 289 (72.6%) had mFDA success at 6-months and 217 (63.1%) at 12 months. Among the 4347 persons on 3DR, 4183 and 3386 had follow-up data available at 6- and 12-months respectively, with similar proportions of mFDA success at 6- (69.7%) and 12-months (59.3%, p=0.2; Fig. 1).

In the univariate analyses, there were no significant differences in the odds of mFDA success at either 6- or 12-months with similar results in multivariable analysis at both time points (Fig. 2). Baseline VL ≥400 cp/mL, HIV infection through intravenous drug use, Eastern European region, and lower CD4 count (≤200 cell/μL) were all associated with lower odds of success (data not shown). In a sensitivity analysis when applying a cut-off for mFDA success of <50 cp/mL, we found a small significant difference favouring 2DR in the univariate analysis at 6 months, but not at 12 months. The multivariable analysis was consistent with the main analysis at both time points (Fig. 2).

Regarding immunologic outcomes, there were no significant differences between 2DR and 3DR in the proportion of individuals with a CD4 increase ≥100 cells/μL or a 25% increase in baseline CD4 count at either 6- or 12-months (figure 1). In univariate analyses, there were no differences in the odds ratio of a CD4 increase ≥100 cells/μL at 6- or 12-months comparing the 2DR and 3DR, whereas in the multivariable analysis there was a small, but statistically significant higher likelihood of a CD4 increase ≥100 cells/μL at 6 months, but not at 12

months, for the 2DR group. Individuals in the two groups were equally likely to have a 25% increase in baseline CD4 count at both time points (Fig 2).

Virologic and immunologic outcomes of 2DR versus 3DR stratified by treatment status at baseline

Table 3 shows outcomes at 6- and 12-months, stratified by treatment status at baseline, as well as the numbers of those failing according to the different components of the mFDA. Only a small proportion of persons in the 2DR or 3DR groups were ARV-naïve when starting their ARV regimen, while most individuals received the 2DR or 3DR with virological control at baseline. In all strata, individuals in the 2DR group had a similar proportion of mFDA success compared to the 3DR group at both time points, regardless of prior treatment status. The main reasons for mFDA failure were unknown VL or regimen changes in all strata. For those in the 2DR group, five individuals had virological failure at 6 months and five at 12 months (two individuals had virological failure at both time points, i.e. 8 virological failures in all). All except one of these virological failures occurred in individuals starting the 2DR after failing the previous treatment regimen. Similarly, we found a higher proportion of virological failures occurred in individuals treated with 3DR after a previous treatment failure. Among persons with virological failure at baseline, there was a higher percentage with mFDA success in the 2DR at 6 months, compared to 3DR (68.1%, 52.9-80.9 vs. 47.1%, 43.1-51.2), but there was no significant difference at 12 months (52.3%, 36.7-67.5 vs. 40.3%, 36.3-44.4).

Incidence of clinical events

We observed a similar incidence of clinical events during follow-up after starting a 2DR (934 PYFU; median FU 1.7 years, IQR 0.8-3.5 years) or 3DR (11583 PYFU; median FU 2.5 years, IQR: 1.1-4.0 years). In the 2DR group there were 40 clinical events (three AIDS-

defining events, 14 NADM, six CVD, five LRE and 12 CKD), giving an incidence rate (IR) of 42.8 events/1000 PYFU (CI 31.4-58.4). Individuals on 3DR had 356 events (69 AIDS-defining events, 83 NADM, 48 CVD, 38 LRE and 118 CKD, IR 30.7/1000 PYFU, CI 27.7-34.1). There were 11 deaths during FU in the 2DR group (IR 11.8/1000 PYFU, CI 95% 5.9-21.1) and 127 deaths (IR 11.8/1000 PYFU, CI 95% 9.2-13.1) in the 3DR group. Although the IRs were somewhat higher in the 2DR group, the individuals had more comorbidities at baseline, while the analysis was not powered to perform formal adjusted comparisons for these.

Discussion:

We here present data from the large, multicentre observational EuroSIDA cohort, examined uptake of and factors associated with starting or switching to a 2DR and assessed virologic and immunologic outcomes for individuals on 2DRs compared to 3DRs. Most of the 2DRs included DRV, RAL or DTG, were largely used by older individuals who were virologically suppressed and immunologically stable with high cumulative ARV experience, and many had either existing or were at high risk of developing comorbidities. Treatment with 2DRs yielded similar virological and immunological outcomes compared to 3DR at both 6- and 12-months.

Individuals in the 2DR group were more likely to be from Southern Europe and less likely to be from Eastern or Northern Europe when compared to Western Europe. Though different socioeconomic, logistic and infrastructural circumstances across Eastern Europe are a reasonable explanation,[26] in Northern Europe it might imply a more conservative approach to the use of 2DR. This would be consistent with the first recommendations of 2DR treatment found in clinical guideline from 2014.[27] In Southern Europe, 2DR may be more commonly used due to lower cost and/or clinicians being more experienced with 2DRs, as many preliminary studies on this treatment strategy come from this region. After adjustment, comorbidities such as ESRD and CVD were associated with starting or switching to a 2DR,

although age was not, suggesting that 2DR were selected based on underlying comorbidities in virologic and immunologic stable persons independent of their age.

We found no evidence that individuals treated with 2DRs had inferior virologic outcomes at 6-or 12-months compared to 3DRs. There were no statistically significant differences in the overall proportion of individuals with mFDA success, across a range of sensitivity analyses, including pre-planned sub-group analyses according to treatment status at baseline. There was some evidence of a better mFDA success at 6 months in those starting a 2DR after previous virologic failure. These results should, however, be interpreted with caution as the difference was small and based on comparatively modest numbers, and we were not able to perform a multivariable analysis. We did not find the same association at 12 months, though this may reflect clinical intervention to ineffective treatment at 6 months, or the relatively small number of individuals in this stratum. These findings are in line with results from RCTs. LPV/r or DRV/r in combination with 3TC[7, 19] or RAL[28, 29] have been shown to be non-inferior compared 3DRs. For INSTI + NNRTI combinations, there is some evidence that RAL+ETR is a promising strategy,[18] while other trials have shown DTG + RPV to be an effective combination for maintaining viral suppression[13]. Likewise, positive results with DTG + 3TC were reported in a recent study from France,[30] and will be investigated further in a planned trial (ClinicalTrials.gov Identifier: NCT03446573). DTG + 3TC could also be a viable treatment option for ARV-naïve individuals based on reports from recent trials.[15]

Regarding immunologic responses, many individuals switched to a 2DR with virologic suppression and a high CD4 count (>500 cells/μL). Therefore, the proportions of individuals with the specified increases in CD4 counts (>100 cells/μL or a >25% increase) were generally low (<30% of individuals). As with the mFDA success, we did not observe any statistically significant differences in the proportion of individuals with a 100 cells/μL CD4

cell increase between the two groups at 12 months. There was a small but statistically significant higher proportion of persons with a CD4 cell increase >100 cells/μL at 6 months in the 2DR group, but this was not significant in the alternative analysis for a 25% increase in CD4 cells. The association may be due to chance. However, the small difference seen at 6 months did not persist to 12 months, suggesting that any effect, if real, is transient and unlikely to translate into a clinical benefit.

The large size of the EuroSIDA study and inclusion of a heterogeneous, geographically diverse population of PLWHIV in real-life clinical settings are major strengths of this analysis. Another strength is that we included a variety of different 2DRs, reflecting the combinations in use in routine clinical care within the time period.

Due to the observational nature of this study, confounding by indication can never be fully excluded. However, the main limitation of this study is, that even in this large cohort, 2DRs were rarely used in the period of the analysis, and we could therefore not perform analyses of specific regimens. Another limitation of the study is that we did not have information on ARV-resistance. Although only eight individuals in the 2DR group experienced virological failure, we were unable to clarify whether this was due to the occurrence of resistance.

A further limitation is that we only considered the first 2DR of each individual in the time period from 1/7/2010 to 31/12/2016. Consequently, if an individual switched from an older 2DR, to another 2DR consisting of more contemporary drugs, the later regimen would not have been included. Also, due to low numbers and limited follow-up, we did not have enough power to adjust for relevant factors or do a formal adjusted analysis or comparison of the incidence of clinical events between the 2DR- and 3DR groups. To sufficiently evaluate and compare long-term clinical outcomes of using 2DR versus 3DR, studies with more extended follow-up is needed.

In conclusion, we found that the 2DRs in our analysis were largely used according to the current clinical guidelines. Our results show that 2DRs in the period were mainly prescribed to ARV-experienced individuals who switched from their previous regimen with virologic suppression, high CD4 counts and pre-existing or higher risk of co-morbidities. Although we observed favourable outcomes for ARV-naïve individual starting a 2DR, the numbers were too low to allow meaningful conclusions. Overall, virologic and immunologic outcomes in individuals on 2DRs were similar to individuals on 3DRs in this selected population, in line with results from randomized clinical trials, although confounding by indication cannot be fully excluded.

Acknowledgements.

Author contributions: BN drafted the first manuscript in close collaboration with APM. APM conducted the statistical analysis and prepared all figures for the manuscript. AM, LR and JL supervised the projected. EF, LP AR, VS, AC, TB, VM, SM, MB, JB, RM, TT, DE, MK, VV, GB, TS, LR and VV provided data for the analyses and/or significant scientific input to the project in accordance with the ICMJE criteria.

The multi-center study group, EuroSIDA (national coordinators in parenthesis).

Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires.

Austria: (B Schmied), Otto Wagner Hospital, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck.

Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk.

Belgium: (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent.

Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo.

Croatia: (J Begovac), University Hospital of Infectious Diseases, Zagreb.

Czech Republic: (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen.

Denmark: G Kronborg, T Benfield, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, Rigshospitalet, Copenhagen; C Pedersen, IS Johansen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, L Wiese, NF Moller, Sjællands Universitetshospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod.

Estonia: (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve.

Finland: (M Ristola), I Aho, Helsinki University Central Hospital, Helsinki.

France: (J-P Viard), Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; C Pradier, E Fontas, Hôpital de l'Archet, Nice; C Duvivier, Hôpital Necker-Enfants Malades, Paris.

Germany: (J Rockstroh), Universitäts Klinik Bonn; G Behrens, Medizinische Hochschule Hannover; O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; C Stefan, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne.

Georgia: (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi

Greece: (H Sambatakou), Ippokration General Hospital, Athens; G Adamis, N Paissios, Athens General Hospital "G Gennimatas"

Hungary: (J Szlávik), Szent László Hospital, Budapest.

Iceland: (M Gottfredsson), Landspitali University Hospital, Reykjavik.

Ireland: (F Mulcahy), St. James's Hospital, Dublin.

Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, ZM Sthoeger, AIDS Center (Neve Or), Jerusalem.

Italy: (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan.

Latvia: (B Rozentale), Infectology Centre of Latvia, Riga.

Lithuania: (V Uzdaviniene) Vilnius University Hospital Santaros Klinikos, Vilnius; R Matulionyte, Centro poliklinika, Vilnius, Vilnius University Hospital Santaros Klinikos, Vilnius.

Luxembourg: (T Staub), R Hemmer, Centre Hospitalier, Luxembourg.

Netherlands: (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam.

Norway: (DH Reikvam), A Maeland, J Bruun, Oslo University Hospital, Ullevaal

Poland: (B Knysz), J Gasiorowski, M Inglot, Medical University, Wroclaw; E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; R Flisiak, A Grzeszczuk, Medical University, Bialystok; M Parczewski, K Maciejewska, B Aksak-Was, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; T Smiatacz, M Gensing, Medical University, Gdansk; E Jablonowska, J Kamerys, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz; I Mozer-Lisewska, B Rozplochowski, Poznan University of Medical Sciences, Poznan.

Portugal: (L Caldeira), Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon.

Romania: (R Radoi), C Oprea, Carol Davila University of Medicine and Pharmacy Bucharest, Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest

Russia: (A Panteleev), O Panteleev, St Petersburg AIDS Centre, St Peterburg; A Yakovlev, Medical Academy Botkin Hospital, St Petersburg; T Trofimora, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology named after Academician I.N. Blokhina, Nizhny Novogrod; E Borodulina, E Vdoushkina, Samara State Medical University, Samara.

Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade.

Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana.

Spain: (JM Miró), J. Mallolas, E. Martinez, F. Garcia, JL Blanco, M. Laguno and M. Martinez-Rebollar, Hospital Clinic – IDIBAPS. University of Barcelona, Barcelona; S Moreno, S. del Campo, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, J Puig, JM Llibre, JR Santos, Infectious Diseases Unit & IrsiCaixa AIDS Research Institute, Hospital germans Trias I Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz.

Sweden: (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; CJ Treutiger, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö.

Switzerland: (A Scherrer), R Weber, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen.

Ukraine: A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv.

United Kingdom: (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

The following centers have previously contributed data to EuroSIDA:

Infectious Diseases Hospital, Sofia, Bulgaria

Hôpital de la Croix Rousse, Lyon, France

Hôpital de la Pitié-Salpétière, Paris, France

Unité INSERM, Bordeaux, France

Hôpital Edouard Herriot, Lyon, France

Bernhard Nocht Institut für Tropenmedizin, Hamburg, Germany

1st I.K.A Hospital of Athens, Athens, Greece

Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy

Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy

Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy

Dérer Hospital, Bratislava, Slovakia

Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain

Kiev Centre for AIDS, Kiev, Ukraine

Luhansk State Medical University, Luhansk, Ukraine

Odessa Region AIDS Center, Odessa, Ukraine

Statistical Staff: A Mocroft, A Phillips, A Cozzi-Lepri, L Shepherd, S Amele, A Pelchen-Matthews, A Roen

Steering Committee: I Karpov, M Losso, J Lundgren, J Rockstroh, I Aho, LD Rasmussen, V Svedhem, G Wandeler, C Pradier, N Chkhartishvili, R Matulionyte, C Oprea, JD Kowalska, J Begovac, JM Miró, G Guaraldi, R Paredes

References:

1. European AIDS Clinical Society Guidelines, version 9.1, 2018

2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services, 2018

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

3. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis 2011; 53(11):1120-1126.

4. Holtzman C, Armon C, Tedaldi E, Chmiel JS, Buchacz K, Wood K, et al. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. J Gen Intern Med 2013; 28(10):1302-1310.

5. Troya J, Bascunana J. Safety and Tolerability: Current Challenges to Antiretroviral Therapy for the Long-Term Management of HIV Infection. AIDS Rev 2016; 18(3):127-137.

6. Pelchen-Matthews A, Ryom L, Borges AH, Edwards S, Duvivier C, Stephan C, et al. Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. AIDS 2018; 32(16):2405-2416.

7. Arribas JR, Girard PM, Landman R, Pich J, Mallolas J, Martinez-Rebollar M, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. Lancet Infect Dis 2015; 15(7):785-792.

8. Di Giambenedetto S, Fabbiani M, Quiros Roldan E, Latini A, D'Ettorre G, Antinori A, et al. Treatment simplification to atazanavir/ritonavir + lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48

week results from a randomized trial (ATLAS-M). J Antimicrob Chemother 2017; 72(4):1163-1171.

9. Perez-Molina JA, Rubio R, Rivero A, Pasquau J, Suarez-Lozano I, Riera M, et al. Simplification to dual therapy (atazanavir/ritonavir + lamivudine) versus standard triple therapy [atazanavir/ritonavir + two nucleos(t)ides] in virologically stable patients on antiretroviral therapy: 96 week results from an open-label, non-inferiority, randomized clinical trial (SALT study). J Antimicrob Chemother 2017; 72(1):246-253.

10. Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV 2015; 2(4):e127-136.

11. Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012; 379(9835):2439-2448.

12. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013; 369(19):1807-1818.

13. Llibre JM, Hung CC, Brinson C, Castelli F, Girard PM, Kahl LP, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet 2018.

14. Maggiolo F, Di Filippo E, Valenti D, Serna Ortega PA, Callegaro A. NRTI Sparing Therapy in Virologically Controlled HIV-1 Infected Subjects: Results of a Controlled, Randomized Trial (Probe). J Acquir Immune Defic Syndr 2016; 72(1):46-51.

15. Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2018.

16. Figueroa M, Sued O, Gun A, Belloso W, Cecchini D, Lopardo G, et al. DRV/R/3TC FDC for HIV-1 Treatment Naive Patients: Week 48 Results of the Andes Study. In: Conference on Retroviruses and Opportunistic Infections Edited by Abstract ML-O. Boston, Massachusetts; 2018.

17. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczer D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 2017; 390(10101):1499-1510.

18. Katlama C, Reynes J, Assoumou L, Valantin M, Beniguel L, Soulie C, et al. Efficacy of a Maintenance Strategy with Raltegravir/Etravirine: the ANRS 163 ETRAL trial. IAS 2017, Paris.

19. Pulido F, Ribera E, Lagarde M, Perez-Valero I, Palacios R, Iribarren JA, et al. Dual Therapy With Darunavir and Ritonavir Plus Lamivudine vs Triple Therapy With Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 Viral Suppression: Randomized, Open-Label, Noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial. Clin Infect Dis 2017; 65(12):2112-2118.

20. Borghetti A, Baldin G, Ciccullo A, Gagliardini R, D'Avino A, Mondi A, et al. Virological control and metabolic improvement in HIV-infected, virologically suppressed patients switching to lamivudine/dolutegravir dual therapy. J Antimicrob Chemother 2016; 71(8):2359-2361.

21. Capetti AF, Cossu MV, Orofino G, Sterrantino G, Cenderello G, De Socio GV, et al. A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. BMC Infect Dis 2017; 17(1):658.

22. Capetti AF, Cossu MV, Sterrantino G, Barbarini G, Giambenedetto SD, De Socio GV, et al. Dolutegravir Plus Rilpivirine as a Switch Option in cART-Experienced Patients: 96-Week Data. Ann Pharmacother 2018:1060028018761600.

23. Maggiolo F, Gulminetti R, Pagnucco L, Digaetano M, Benatti S, Valenti D, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. BMC Infect Dis 2017; 17(1):215.

24. Friis-Moller N, Thiebaut R, Reiss P, Weber R, Monforte AD, De Wit S, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil 2010; 17(5):491-501.

25. Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. PLoS Med 2015; 12(3):e1001809.

26. Reekie J, Kowalska JD, Karpov I, Rockstroh J, Karlsson A, Rakhmanova A, et al. Regional differences in AIDS and non-AIDS related mortality in HIV-positive individuals across Europe and Argentina: the EuroSIDA study. PLoS One 2012; 7(7):e41673.

27. EACS European AIDS Clinical Society Guidelines, version 7.1, 2014.

28. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Endo T, Horiba M, et al. Switching tenofovir/emtricitabine plus lopinavir/r to raltegravir plus Darunavir/r in patients with suppressed viral load did not result in improvement of renal function but could sustain viral suppression: a randomized multicenter trial. PLoS One 2013; 8(8):e73639.

29. Ofotokun I, Sheth AN, Sanford SE, Easley KA, Shenvi N, White K, et al. A switch in therapy to a reverse transcriptase inhibitor sparing combination of lopinavir/ritonavir and

raltegravir in virologically suppressed HIV-infected patients: a pilot randomized trial to assess efficacy and safety profile: the KITE study. AIDS Res Hum Retroviruses 2012; 28(10):1196-1206.

30. Joly V, Burdet C, Landman R, Vigan M, Charpentier C, Katlama C, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). J Antimicrob Chemother 2019; 74(3):739-745.

Table 1: Baseline demographic and baseline clinical characteristics

		2DR		3DR		Total		
		n =	(	n =	(%	n =	(%	P-
Age Group	>50 yrs	252	(6	1565	(3	18	(3	<0.00
Gender	Male	314	(7	3081	(7	33	(7	0.1
Ethnic Group	White	368	(8	3767	(8	41	(8	0.8
Region of Europe*	Southern	195	(4	1059	(2	12	(2	<0.00
	Western/Central	131	(3	1146	(2	12	(2	01
	Northern	55	(1	776	(1	83	(1	
	Eastern	42	(1	1366	(3	14	(3	
BMI (kg/m^2)	Underweight	30	(7	152	(4)	18	(4)	<0.00
	Overweight (25	91	(2	908	(2	99	(2	01
	Obese (> 30)	25	(6	247	(6)	27	(6)	
	unknown	59	(1	1060	(2	11	(2	
Smoking status[¤]	Never smoked	140	(3	1314	(3	14	(3	0.003
	Current smoker	165	(3	2004	(4	21	(5)	2
Mode of infection	MSM	164	(3	1590	(3	17	(3	0.6
	IDU	105	(2	1159	(2	12	(2	
	Heterosexual	117	(2	1262	(2	13	(2	
	Other or	37	(9	336	(8)	37	(8)	
HIV Diagnosis	< 2 yrs before	5	(1	267	(6)	27	(6)	<0.00
	unknown	19	(5	503	(1	52	(1	01
Baseline VL (cp/mL)	< 400	370	(8	3235	(7	36	(7	<0.00
Baseline CD4 cell counts	> 500	250	(6	2373	(5	26	(5	0.02
	350 - 500	88	(2	835	(1	92	(1	
(Cells/µL)	200 - 350	46	(1	722	(1	76	(1	
	< 200	39	(9	417	(1	45	(1	
Previous exposure to ARVs	Previously	415	(9	3781	(8	41	(8	<0.00
	Naïve	8	(2	566	(1	57	(1	01
Number of ARV drugs	1 to 4	57	(1	1179	(2	12	(2	<0.00
previously exposed to	> 5	357	(8	2595	(6	29	(6	01
Previous exposure to specific ARV	NRTI	409	(9	3740	(8	41	(8	<0.00
	NNRTI	286	(6	2389	(5	26	(5	<0.00
	PI/b	339	(8	2542	(5	28	(6	<0.00
	INSTI	115	(2	268	(6)	38	(8)	<0.00
Hepatitis B	HBsAg positive	16	(4	194	(5)	21	(4)	0.1
	Not tested /	39	(9	547	(1	58	(1	
Hepatitis C virus	Hepatitis C ab	161	(3	1800	(4	19	(4	0.000
	Not tested /	12	(3	299	(7)	31	(7)	6
Hypertension	yes	247	(5	2081	(4	23	(4	<0.00
	Unknown	22	(5	141	(3)	16	(3)	01
Dyslipidaemia	yes	334	(7	2594	(6	29	(6	<0.00
	unknown	4	(1	193	(4)	19	(4)	01
Chronic Kidney Disease	yes	41	(1	139	(3)	18	(4)	<0.00
	unknown	6	(1	195	(5)	20	(4)	unkn
Family history of CVD	yes	35	(8	300	(7)	33	(7)	<0.00
	unknown	143	(3	1088	(2	12	(2	01
CVD	yes	31	(7)	171	(4)	202	(4)	<0.00 01
Diabetes	yes	46	(1	211	(5)	25	(5)	0.000
NADM	yes	28	(7	148	(3)	17	(4)	0.000
ESRD	yes	6	(1	8	(0	14	(0	<0.00

[¤] Past and unknown smoking status: 102 and 16 individuals and in the 2DR group, 798 and 231 in the 3DR group respectively.

*Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East: Belarus, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovenia and Ukraine.

Abbreviations; MSM: Men-sex-with-men, IDU: Injecting drug use, (N)NRTIs: (non)Nucleot(s)ide reverse transcriptase inhibitor, PI/b: Boosted protease inhibitor, INSTI: Integrase inhibitor, ARV: Antiretroviral drugs, CVD: Cardiovascular disease, HBsAg: Hepatitis B surface antigen, NADM: non-AIDS defining malignancy, ESRD: end-stage renal disease

Table 2: Univariate and multivariable analysis of factors associated with starting or switching to a 2DR.

		Univariate analysis			Multivariable analysis		
		Odds ratio	95% CI	P-value	Adjusted Odds ratio	95% CI	P-value
Age Group	≥ 50 yrs (vs. < 50 yrs)	2.62	2.14-3.21	<0.0001	1.19	0.90 - 1.56	0.2
Region of Europe	**Western/Central**	1			1		
	Southern	1.61	1.27-2.04	<0.0001	1.76	1.35 - 2.29	<0.0001
	Northern	0.62	0.45-0.86	0.004	0.64	0.45 - 0.91	0.0129
	Eastern	0.27	0.19-0.38	<0.0001	0.42	0.28 - 0.62	<0.0001
Baseline VL	≥ 400 cp/mL (vs. < 400 cp/mL)	0.42	0.1-0.56	<0.0001	1.00	0.69 - 1.44	1.0
Baseline CD4 cell counts category	**> 500 Cells/µL**	1			1		
	200 - 350 Cells/µL	0.61	0.44-0.84	0.002	0.77	0.53 - 1.10	0.1
	< 200 Cells/µL	0.89	0.62-1.26	0.5	1.39	0.91 - 2.13	0.1
Previous ARV exposure	ARV naïve (vs. experienced)	0.13	0.06-0.26	<0.0001	0.39	0.11 - 1.38	0.1
Previous exposure to	NRTIs (vs. never exposed)	4.74	2.76-8.13	<0.0001	0.61	0.22 - 1.67	0.3
	NNRTIs	1.71	1.38-2.12	<0.0001	1.14	0.90 - 1.44	0.3
	PI/r	3.13	2.35-4.17	<0.0001	1.97	1.49 - 2.60	<0.0001
	INSTIs	5.68	4.44-7.28	<0.0001	3.24	2.47 - 4.26	<0.0001
BMI (Kg/m²)	**Normal weight (18.5 to < 25)**	1			1		
	Underweight (< 18.5)	1.79	1.18-2.72	0.006	1.76	1.11 - 2.79	0.02
	Overweight (25 to < 30)	0.91	0.70-1.18	0.5	0.83	0.63 - 1.09	0.2
	Obese (≥ 30)	0.92	0.60-1.42	0.7	0.83	0.52 - 1.32	0.4
Smoking status	Current smoker (vs. never)	0.77	0.61-0.98	0.03	0.70	0.53 - 0.92	0.01
ESRD	Yes (vs. no)	7.81	2.7-22.62	<0.0001	7.17	2.18 – 23.6	0.0006
CKD3[#]	**No**	1					
	Yes	3.15	2.19-4.53	<0.0001			
D:A:D 5 yr CVD risk	**Low (<1%)**	1			1		
	Medium (1-5%)	1.52	1.08-2.14	0.02	1.08	0.72 - 1.62	0.7
	High (5-10%)	3.35	2.35-4.78	<0.0001	2.07	1.27 - 3.40	0.004
	Very High (>10%)	4.21	2.91-6.10	<0.0001	2.39	1.39 - 4.12	0.002

*Adjusted for: Age group, gender, region of Europe, BMI, smoking status, recent HIV diagnosis, prior AIDS-defining disease, baseline CD4 cell count, baseline viral load, previous exposure to ARVs or naïve, previous exposure to NRTIs, NNRTIs, PI/b, INSTIS or other ARVs, ESRD, family history of CVD and D:A:D 5-year CVD risk factor score.

[#]Not included in the multivariable analysis due to collinearity with ESRD. When included instead of ESRD; aOR 1.66, CI95%: 1.10-2.50, P= 0.0162.

Table 3: Immunologic response, on-treatment- and mFDA success and reasons for mFDA failure at 6- and 12-months ± 16 weeks stratified by treatment status at baseline:

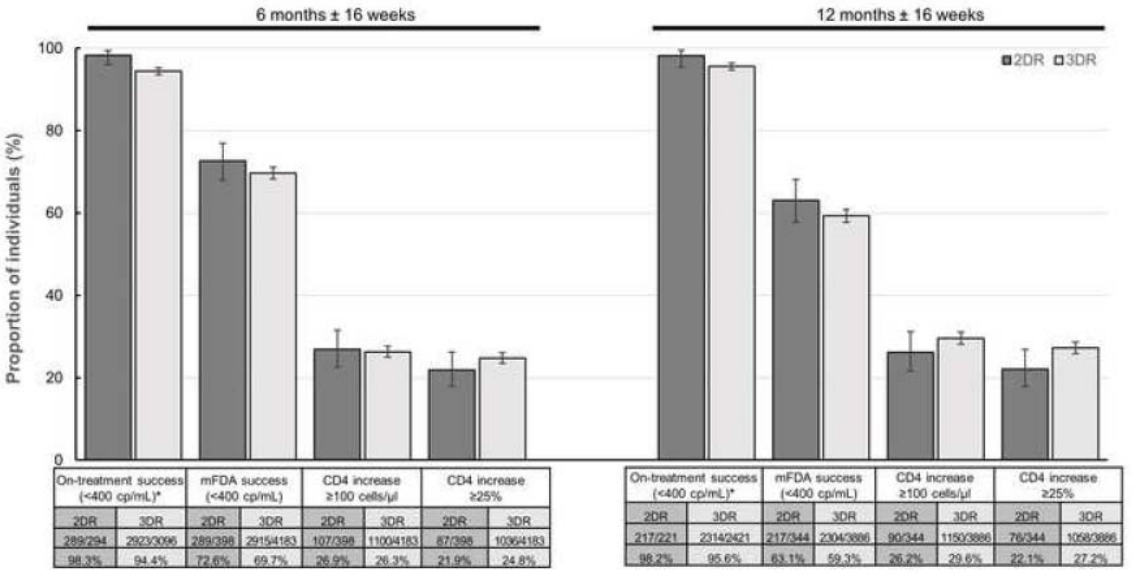
			6 monhts ± 16 weeks						12 months ± 16 weeks					
		Treatment status at baseline	2DR, n = 398			3DR, n = 4183			2DR, n = 344			3DR, n = 3886		
			n	%*	CI 95%	n	%*	CI 95%	n	%*	CI 95%	n	%*	CI 95%
CD4 cell response: ≥ 100 cells/μL increase		Naïve	5	62.5	24.5 - 91.5	269	48.6	44.4 - 52.9	5	71.4	29.0 - 96.3	286	55.1	50.7 - 59.4
		Controlling	85	24.8	20.3 - 29.7	621	20.5	19.1 - 22.0	74	25.3	20.4 - 30.6	654	23.5	21.9 - 25.1
		Failing	17	36.2	22.7 - 51.5	210	34.7	30.9 - 38.7	11	25.0	13.2 - 40.3	210	35.9	32.0 - 39.9
On-treatment success: <400 cp/mL[#]		Naïve	6	100	54,1 - 100	360	90,7	87,4 - 93,4	5	100	47,8 - 100	296	94,3	91,1 - 96,6
		Controlling	251	100	98,5 - 100	2273	98,5	97,9 - 98,9	189	99,5	97,1 - 100	1777	98,7	98,1 - 99,2
		Failing	32	86,5	71,2 - 95,5	290	74,2	69,5 - 78,4	23	88,5	69,9 - 97,6	241	78,5	73,5 - 83
mFDA success < 400 cp/mL		Naïve	6	75.0	34.9 - 96.8	358	64.7	60.6 - 68.7	5	71.4	29.0 - 96.3	294	56.7	52.3 - 61.0
		Controlling	251	73.2	68.2 - 77.8	2272	75.1	73.5 - 76.6	189	64.5	58.7 - 70.0	1774	63.8	62.0 - 65.6
		Failing	32	68.1	52.9 - 80.9	285	47.1	43.1 - 51.2	23	52.3	36.7 - 67.5	236	40.3	36.3 - 44.4
mFDA Failure[¤]	VL failure: ≥400 cp/mL[#]	Naïve	0	0.0	0.0 - 36.9	50	9.0	6.8 - 11.8	0	0.0	0 - 41.0	38	7.3	5.2 - 9.9
		Controlling	0	0.0	0.0 - 1.1	46	1.5	1.1 - 2.0	1	0.3	0.0 - 1.9	44	1.6	1.2 - 2.1
		Failing	5	10.6	3.6 - 23.1	132	21.8	18.6 - 25.3	4	9.1	2.5 - 21.7	106	18.1	15.1 - 21.5
	Unknown VL in the time frame	Naïve	1	12.5	0.32 - 52.7	87	15.7	12.8 - 19.0	2	28.6	3.7 - 71.0	111	21,4	17.9 - 25.2
		Controlling	7	14.9	6.2 - 28.3	120	19.8	16.7 - 23.2	13	29.6	16.8 - 45.2	165	28,2	24.6 - 32.0
		Failing	50	14.6	11.0 - 18.8	400	13.2	12.0 - 14.5	54	18.4	14.2 - 23.4	476	17,1	15.7 - 18.6
	Regimen changes	Naïve	1	12.5	0.3 - 52.7	90	16.3	13.3 - 19.6	1	14.3	0.4 - 57.9	126	24.3	20.7 - 28.2
		Controlling	47	13.7	10.2 - 17.8	348	11.5	10.4 - 12.7	63	21.5	16.9 - 26.7	568	20.4	18.9 - 22.0
		Failing	3	6.4	1.3 - 17.5	110	18.2	15.2 - 21.5	8	18.2	8.2 - 32.7	166	28.4	24.8 - 32.2
	AIDS-defining event	Naïve	0	0.0	0.0 - 36.9	12	2.2	1.1 - 3.8	0	0.0	0.0 - 41.0	9	1.7	0.8 - 3.3
		Controlling	0	0.0	0.0 - 1.1	3	0.1	0.0 - 0.3	0	0.0	0.0 - 1.3	5	0.2	0.1 - 0.4
		Failing	1	2.1	0.1-11.3	9	1.5	0.7-2.8	1	2.3	0.1 – 12.0	16	2.7	1.6 – 4.4
	Death	Naïve	0	0.0	0.0 - 36.9	5	0.9	0.3 - 2.1	0	0.0	0.0 - 41.0	6	1.2	0.4 - 2.5
		Controlling	0	0.0	0.0 - 1.1	14	0.5	0.3 - 0.8	1	0.3	0.0 - 1.9	25	0.9	0.6 - 1.3
		Failing	1	2.1	0.1 - 11.3	8	1.3	0.6 - 2.6	1	2.3	0.1 - 12.0	14	2.4	1.3 - 4.0

*Percentage of total in specific treatment strata

[#] Proportion of individuals with known viral load and without regimen change whom achieved virologic success (VL <400 cp/mL) at 6- or 12-months follow-up

[¤] mFDA failure: ≥1 of VL > 400 cp/mL, unknown viral load in the timeframe, regimen change, AIDS event or death during follow-up

Figure 1: Proportions of virologic success, mFDA success and immunologic responses 6- or 12-months ± 16 weeks after starting or switching to a 2DR or 3DR.



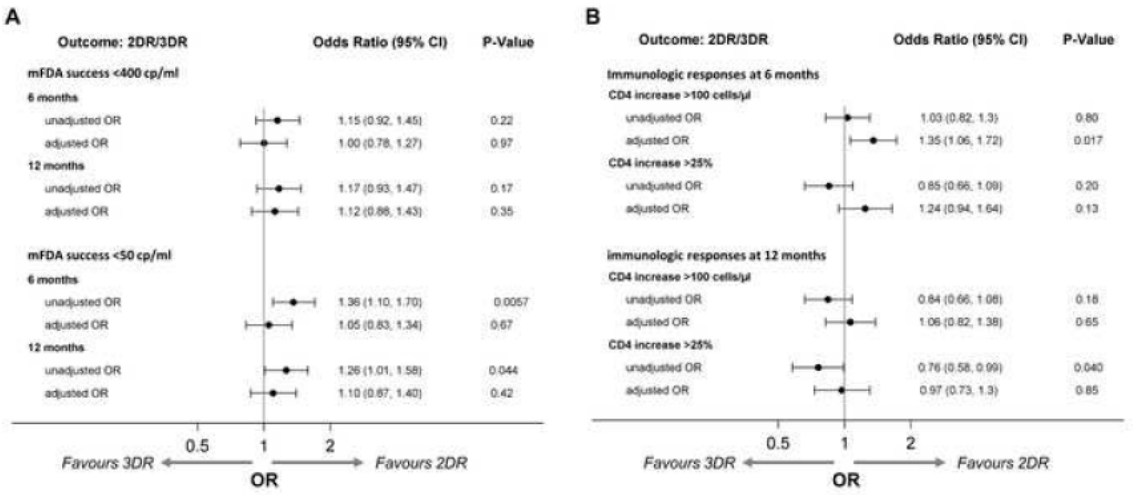
On-treatment success (<400 cp/mL)*		mFDA success (<400 cp/mL)		CD4 increase ≥100 cells/µl		CD4 increase ≥25%	
2DR	3DR	2DR	3DR	2DR	3DR	2DR	3DR
289/294	2923/3096	289/398	2915/4183	107/398	1100/4183	87/398	1036/4183
98.3%	94.4%	72.6%	69.7%	26.9%	26.3%	21.9%	24.8%

On-treatment success (<400 cp/mL)*		mFDA success (<400 cp/mL)		CD4 increase ≥100 cells/µl		CD4 increase ≥25%	
2DR	3DR	2DR	3DR	2DR	3DR	2DR	3DR
217/221	2314/2421	217/344	2304/3886	90/344	1150/3886	76/344	1058/3886
98.2%	95.6%	63.1%	59.3%	26.2%	29.6%	22.1%	27.2%

Bars show 95% confidence intervals (CI) of proportions.

*VL are shown for individuals who had a measurement available at 6-or 12-months ±16 weeks and who did not change regimen at 6- or 12-months follow-up. This included 294 individuals in the 2DR group and 3096 individuals on 3DR at 6 months (10-42 weeks) and 221 and 2421 individual, respectively, at 12 months (36-68 weeks).

Figure 2: Forest plots of the OR and aOR for obtaining a virologic success < 400- or < 50 cp/mL by mFDA and a CD4 increase >100 cells /µL or a 25% increase in CD4 count from baseline, at 6- or 12-months ± 16 weeks respectively.



A: Odds ratio and adjusted odds ratio of mFDA success at 6-and 12-months ± 16 weeks depending on being on a 2DR or 3DR. Top half shows mFDA defined as < 400 cp/mL. Bottom half shows the sensitivity analysis defining mFDA as < 50 cp/mL.

B: Odds ratio adjusted odds ratios of immunologic response defined as either CD4 increase of > 100 cells/µL or a CD4 increase of > 25 % from baseline. Top half shows reconstitution at 6 months. Bottom half reconstitution at 12 months.

The models have been adjusted for age group (<50 or ≥50 years), gender, race, region of Europe, mode of transmission, recent HIV diagnosis, baseline CD4 cell counts, baseline viral load, prior ART, liver-related events and chronic kidney disease.