Clinical outcomes of two-drug regimens vs. three-drug regimens in antiretroviral treatment-experienced people living with HIV

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Summary: In this analysis of 9791 antiretroviral-experienced individuals in RESPOND (1088 on two-drug regimens, 8703 on three-drug regimens), there was a similar short-term incidence of severe clinical events after adjusting for baseline characteristics (incidence rate ratio 0.92 [0.72-1.19], p=0.53).

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Abstract

Background

Limited data exist comparing clinical outcomes of two-drug regimens (2DRs) and three-drug regimens (3DRs) in people living with HIV.

Methods

Antiretroviral treatment-experienced individuals in RESPOND switching to a new 2DR or 3DR from 1/1/12-1/10/18 were included. The incidence of clinical events (AIDS, non-AIDS cancer, cardiovascular disease, end-stage liver and renal disease, death) was compared between regimens using Poisson regression.

Results

Of 9791 individuals included, 1088 (11.1%) started 2DRs and 8703 (88.9%) 3DRs. The most common 2DRs were dolutegravir plus lamivudine (22.8%) and raltegravir plus boosted darunavir (19.8%); the most common 3DR was dolutegravir plus 2 nucleoside reverse transcriptase inhibitors (46.9%). Individuals on 2DRs were older (median 52.6 years [interquartile range 46.7-59.0] vs 47.7 [39.7-54.3]), and a higher proportion had ≥1 comorbidity (81.6% vs 73.9%).

There were 619 events during 27,159 person-years of follow-up (PYFU): 540 (incidence rate [IR] 22.5/1000 PYFU [95% CI 20.7-24.5]) on 3DRs, 79 (30.9/1000 PYFU [24.8-38.5]) on 2DRs. The most common events were death (7.5/1000 PYFU [95% CI 6.5-8.6]) and non-AIDS cancer (5.8/1000 PYFU

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[4.9-6.8]). After adjustment for baseline demographic and clinical characteristics, there was a similar incidence of events on both regimen types (2DRs vs 3DRs IR ratio: 0.92 [0.72-1.19]; p=0.53).

Conclusions

This is the first large, international cohort assessing clinical outcomes on 2DRs. After accounting for baseline characteristics, there was a similar incidence of events on 2DRs and 3DRs. 2DRs appear to be a viable treatment option with regard to clinical outcomes; further research on resistance barriers and long-term durability of 2DRs is needed.

Key words: HIV; dual therapy; two-drug regimens; antiretroviral treatment; clinical outcomes

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Introduction

Standard treatment of HIV involves combination antiretroviral therapy (ART), traditionally with three antiretroviral drugs (ARVs) (1). Use of three-drug regimens (3DRs) has been shown to be effective in maintaining viral suppression and increasing CD4 cell counts (2–4). However, ART is a lifelong commitment, and there are concerns around long-term toxicities (5–8). With an aging HIV population, the prevalence of non-AIDS comorbidities is increasing, and it is therefore increasingly important to reduce potential risks associated with ART (8–10).

The emergence of new ARVs with a higher barrier against resistance and more potent antiretroviral activity has led to more interest in reducing ART to two-drug regimens (2DRs). Several clinical trials and observational studies have shown good virological and immunological efficacy of 2DRs (11–19). There are five 2DRs recommended by current treatment guidelines as switch strategies for individuals with a viral load (VL) below the limit of detection and without historical resistance or hepatitis B co-infection: dolutegravir (DTG) plus rilpivirine (RPV), DTG plus lamivudine (3TC), atazanavir (ATV/b) plus 3TC, boosted darunavir (DRV/b) plus 3TC (1,20–22), and DRV/b plus RPV (1). Additionally, DTG plus 3TC is widely recommended as an initial regimen for ART-naïve individuals (1,21,22).

Despite increasing virologic and immunologic evidence supporting 2DRs, there remains little research available on a large, international scale assessing clinical endpoints of 2DRs. Our aim was to compare clinical outcomes with use of 2DRs versus 3DRs.

Methods

Study design and setting

The International Cohort Consortium of Infectious Diseases (RESPOND) is a prospective, multi-cohort collaboration including almost 30,000 people living with HIV-1 (PLWH) from 17 cohorts across Europe and Australia. Further details on RESPOND are published elsewhere (23). Clinical and

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demographic data are collected on participants during routine clinical care at time of enrolment and annually thereafter. Data is also retrospectively collected on the 5 years prior to enrolment, and earlier if available. Data on clinical events including AIDS and non-AIDS defining cancers (ADC and NADC), cardiovascular disease (CVD), end-stage liver and renal disease (ESLD and ESRD), and death are collected in real-time. Events listed above, occurring from 12 months prior to the last cohort visit before RESPOND enrolment onwards are submitted using a case report form (CRF), which are validated by clinicians at the RESPOND coordinating centre using prespecified algorithms (24). Analyses in RESPOND are performed including validated and non-validated events; sensitivity analyses are performed including validated events only.

Participants

Inclusion criteria for RESPOND are detailed elsewhere (25). For this analysis, ART-experienced individuals from RESPOND were included if they switched to an eligible 2DR or 3DR, with or without virologic suppression, after the latest of local cohort enrolment and 1st January 2012. ART-naïve individuals were excluded as most 2DRs are currently recommended as switch strategies (1) and only 3% of those starting 2DRs in RESPOND were ART-naïve. Eligible regimens, as listed in Figure 1, were chosen a priori by a working group to reflect 2DRs currently being prescribed in real-world settings, rather than limited only to those currently recommended. The 3rd drug for 3DRs were chosen to include the same ARVs included in the 2DRs. Individuals were aged ≥18 years at regimen start (defined as baseline) and had a CD4 cell count and VL measurement 12 months prior to or within 12 weeks after starting the regimen of interest. Participants starting an eligible 2DR and 3DR during follow-up (FU) were included in the 2DR group. Participants starting eligible 3DRs were then identified from those not starting 2DRs.

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Outcome definition

The primary outcome was severe clinical event, defined as a composite outcome of AIDS (cancer and non-cancer), NADC, CVD (defined as invasive cardiovascular procedures, myocardial infarction, or stroke), ESLD, ESRD, and death (24). Individuals were followed until the first severe event of any type, last clinical visit, or 1st October 2018 (administrative censoring date), whichever occurred first.

Definitions of potential confounders

The following variables, defined prior to or at regimen start, were considered as potential confounders: year of starting the regimen of interest, age, gender, ethnicity, body mass index, smoking status, geographical region (categorised as in previous RESPOND analyses (26)), HIV risk category, nadir CD4 cell count, CD4 and CD8 cell counts at regimen start, VL at regimen start, number of ARVs and drug classes previously exposed to, and duration of total prior ART. Prior comorbidities considered included viral hepatitis B and C (HBV/HCV), hypertension, diabetes, AIDS, NADC, ESLD, ESRD, CVD, fracture, chronic kidney disease, chronic liver enzyme elevation, and dyslipidaemia. Definitions of all variables are provided in the footnote of Table 1.

Statistical methods

Reasons for discontinuing the previous regimen before starting the 2DR or 3DR were compared where the previous regimen was discontinued within 7 days prior to starting the new regimen.

Poisson regression was used to compare the incidence of any severe clinical event between regimen types, adjusted for baseline characteristics. Each characteristic was adjusted for separately in univariable models and those with p-value <0.1 were simultaneously included in a multivariable model.

Results of the multivariable model were compared according to the reason for discontinuing the previous regimen (toxicity vs other) before starting the 2DR or 3DR. Other prespecified subgroup

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analyses included age, gender, CD4 count, and VL at regimen start. All subgroup analyses were performed by fitting an interaction term between regimen type and the subgroup of interest.

In all models, an unknown category was used to account for missing data. Sensitivity analyses were performed using multiple imputation by chained equations with 10 imputations, including the same variables as those included in the primary analysis model. Results were combined using Rubin's rules (27). A complete case analysis was also performed excluding participants with missing data on any variables included in the model.

Other sensitivity analyses included restricting analyses to include centrally validated events only and comparing 2DRs which are currently recommended in treatment guidelines to matched 3DRs.

Finally, exploratory analyses were performed comparing the incidence of the most common individual events (AIDS [non-cancer], NADC, CVD, death), adjusted for key baseline characteristics (age, CD4 cell count at regimen start, smoking status, and number of ARVs previously exposed to).

Analyses were performed using Stata/SE 15.0 (StataCorp LLC). All p-values are two sided with a p-value <0.05 defined as statistically significant.

Results

Amongst 10,052 eligible RESPOND participants, 9791 (97.4%) met the inclusion criteria and were included in the analysis. A larger proportion of those excluded were injecting drug users compared to those included (26.3% excluded vs 16.4% included); other baseline characteristics were similar. Of those included, 1088 (11.1%) started 2DRs and 8703 (88.9%) started 3DRs. Figure 1 shows the reasons for exclusion of participants and the number included on each regimen. The most common 2DRs were DTG plus 3TC (22.8%), raltegravir (RAL) plus DRV/b (19.8%), and DTG plus DRV/b (18.4%). The most common 3DR was DTG plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) (46.9%); the most common NRTI backbones were tenofovir disoproxil fumarate/emtricitabine (45.0%) and abacavir/3TC (40.5%).

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Baseline characteristics of participants are presented in Table 1. The median age at baseline was higher on 2DRs (52.6 years [interquartile range, IQR, 46.7-59.0] 2DRs vs 47.7 [39.7-54.3] 3DRs, p<0.001). The median time between date of baseline VL measurement and regimen start was 21 days [6-55] and most participants on both regimen types had a suppressed VL (86.4% on 2DRs vs 87.9% on 3DRs, p=0.16). CD4 cell count was also similar (622 cells/µL [409-814] 2DRs vs 605 [424-809] 3DRs, p=0.55). Approximately 89% of participants had at least one comorbidity, mainly driven by dyslipidaemia. There was a higher proportion of most comorbidities in those on 2DRs, including prior CVD (8.0% vs 3.6%, p<0.0001) and NADC (5.1 vs 4.6%, p=0.007). Finally, participants on 2DRs had been exposed to more ARVs prior to starting the regimen of interest (8 ARVs [5-11] vs 6 [4-8], p<0.001).

Of those who started a 2DR or 3DR, 1006 (92.5%) and 8071 (92.7%) discontinued their previous regimen within 7 days of starting the new regimen, respectively. The most common reason for discontinuation of the previous regimen was toxicity for both regimen types (30.9% amongst those on 2DRs vs 31.1% on 3DRs; p=0.91). Amongst those discontinuing for toxicity, the most common type of toxicity was related to nervous system for those starting 3DRs (28.3%) and renal impairment for 2DRs (37.9%). Additionally, treatment simplification was reported for a larger proportion of discontinuations amongst participants starting a 3DR (9.3% 2DRs vs 15.2% 3DRs; p<0.001).

Virologic and immunologic outcomes at 6 and 12 months FU were similar on 2DRs and 3DRs (supplementary material).

Severe clinical outcomes

Median FU was 2.6 years (IQR 1.4-3.8) and higher for those on 3DRs (2.7 [1.4-3.8]) compared to 2DRs (2.2 [1.2-3.2]). During a total FU of 27,159 years, there were 619 severe clinical events (incidence rate [IR] 23.3/1000 PYFU [95% CI 21.6-25.2]): 540 on 3DRs (22.5/1000 PYFU [20.7-24.5]) and 79 on 2DRs (30.9/1000 PYFU [24.8-38.5]). The most common events were death (IR 7.5/1000

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PYFU [6.5-8.6]) and NADC (5.8/1000 PYFU [4.9-6.8]). Figure 2 shows the crude IRs of each event by regimen type. With the exception of death, the crude IR of each event was higher on 2DRs, although some of the event rates have wide confidence intervals due to the small number of events.

The unadjusted IR of any severe event was higher on 2DRs (IR ratio [IRR] 1.37 [95% CI 1.08-1.73], p=0.009), as shown in Figure 3. After adjustment for age, the difference was attenuated and no longer significant (IRR 1.08 [0.85-1.37], p=0.54); results were similar after adjustment for a wide range of baseline characteristics (0.92 [0.72-1.19]; p=0.53). Of the 619 events, 462 were in the validation period, and 444 (96.1%) were validated, giving an IR of validated events of 28.1/1000 PYFU (25.4-31.0) for 3DRs, 34.6/1000 PYFU (26.7-44.7) for 2DRs, and a crude IRR comparing 2DRs to 3DRs of 1.23 (0.93-1.62; p=0.14). Results after adjustment were similar to our main analysis (Figure 3).

In a pre-specified subgroup analysis, there was a significant interaction between regimen type and VL at regimen start (interaction p=0.011); this showed there was no difference in the adjusted incidence of events between regimen types for those with a suppressed VL at regimen start (IRR 1.12 [0.85-1.48]), however in those with uncontrolled viremia (VL≥200 copies/mL), there was a lower incidence of events on 2DRs versus 3DRs (0.51 [0.30-0.89]). Similar results were seen when defining uncontrolled viremia as VL≥50 copies/mL (interaction p=0.03). There was no interaction between the reason for discontinuing the previous regimen (toxicity vs other) and regimen type (interaction p=0.35), indicating a similar incidence of severe events on 2DRs and 3DRs regardless of the reason for discontinuing the previous regimen. Other subgroup analyses were also non-significant.

Exploratory analyses focusing on individual events showed no significant differences between regimen types, however, after adjustment, there was a non-significant higher incidence of AIDS (IRR 1.27 [0.67, 2.43], p=0.47) and NADC (1.35 [0.88, 2.09], p=0.17) on 2DRs, and a lower incidence of CVD (0.80 [0.45, 1.41], p=0.44) and death (0.69 [0.42, 1.12], p=0.13) (Table 2). As the event rates were lower when looking at specific events and the analyses were adjusted for a limited number of

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potential confounders, these estimates have wide confidence intervals, and the results should be interpreted with caution.

Sensitivity analyses

We restricted our analyses to include participants on recommended 2DRs compared to matched 3DRs, as listed in Figure 3 footnote. This included 558 PLWH (51.3%) on 2DRs and 7007 (80.5%) on 3DRs. Differences in baseline characteristics between 2DRs and 3DRs in this analysis were similar to those in the primary analysis, apart from a higher proportion on recommended 2DRs having suppressed VL compared to matched 3DRs (96.1% vs 88.0%, p<0.0001). There were 363 events during 18,133 PYFU on 3DRs (IR 20.0/1000 PYFU [95% CI 18.1-22.2]) and 32 events during 1059 PYFU on 2DRs (30.2/1000 PYFU [21.4-42.7]). There was a similar distribution of events as in the main analysis. As in the primary analysis there was a higher crude incidence of events on 2DRs (IRR 1.51 [95% CI 1.05-2.17], p=0.026; Figure 3); after adjustment there was no longer a significant difference between regimen types (IRR 1.28 [0.88-1.87], p=0.20). Using multiple imputation to account for missing data or performing a complete case analysis showed similar results.

We explored the role of the NRTI backbone for those on 3DRs to investigate whether the incidence of events was driven by the backbone rather than the 3rd drug. We compared the IRs on each 3DR before and after adjusting for the backbone but found similar results. We also repeated the main analysis adjusting for the D:A:D CVD risk score, which accounts for previous exposure to ARVs (28), and found similar results.

We repeated the main analysis using multiple imputation to account for missing data and performed a complete case analysis, both with similar results.

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Discussion

In this study of almost 10,000 ART-experienced individuals (1088 on 2DRs) from across Europe and Australia, we found a similar incidence of severe clinical events on 2DRs versus 3DRs, after adjusting for baseline characteristics, primarily age. While several surrogate markers for clinical outcomes, such as inflammation, and immune activation biomarkers have been extensively compared between 2DRs and 3DRs, with mixed results found (11,16,29,30), this is one of the first large studies comparing clinical outcomes. Baseline characteristics were notably different between groups, suggesting there is likely to be confounding by indication. However, our result was consistent across a wide range of sensitivity analyses, including restricting the analysis to centrally validated events and to individuals starting recommended regimens only.

Subgroup analyses showed consistent results amongst those with a suppressed VL at regimen start. Interestingly, there was a lower incidence of events on 2DRs versus 3DRs in those with uncontrolled viremia, although this group did include smaller numbers. This may be because the proportion of participants with comorbidities amongst those with uncontrolled viremia on 2DRs was lower than amongst those with a suppressed VL, which was not the case for those on 3DRs. However, further research is needed to investigate this further.

For the primary analysis, we included all 2DRs shown to be non-inferior to 3DRs, regardless of whether they are recommended in guidelines, to reflect current clinical practice across the regions included. Sensitivity analyses were performed including 2DRs recommended in international guidelines only, which showed a higher, although non-significant incidence of clinical events on 2DRs. This analysis, however, included considerably smaller numbers and the results have wide confidence intervals. It is expected that there may be a higher short-term incidence of events on 2DRs, as older individuals and those with comorbidities were more likely to be prescribed 2DRs in our analysis; therefore, further research of clinical outcomes with longer FU on 2DRs is needed.

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Results from pre-planned exploratory analyses comparing the incidence of individual events suggest that NADC and non-cancer AIDS event rates may be higher for 2DR, but death and CVD rates lower. These analyses were limited by power and larger studies or studies focused on these endpoints alone are needed to investigate this further. Van Wyck et al. (30) and Calza et al. (31) showed a decrease in lipids with DTG plus 3TC and RAL plus etravirine, respectively, compared to 3DRs, suggesting the risk of CVD could be lower on 2DRs. Although other studies comparing lipids on 2DRs have shown mixed results (11,12,16). Additionally, Serrano-Villar et al. found increased long-term inflammation on 2DRs (32), the clinical implications of which warrant further investigation.

Switching from 3DRs to 2DRs has several potential advantages. Avoiding ARVs shown to be associated with an increased risk of toxicities, such as renal and bone toxicities, may further lead to fewer toxicities on 2DRs, although this requires further research with longer FU and comparison with newer 3DRs such as those including tenofovir alafenamide (11,33–35). Additionally, 2DRs provide a simpler regimen for those not currently on fixed combination pills, and some 2DRs have been shown to be more cost effective than many 3DRs (1,8,34,36). Whilst most treatment guidelines recommend specific 2DRs as switch strategies, DTG plus 3TC is now recommended as a possible initial regimen for ART-naïve individuals (1,20,22). It is therefore important to compare the longer-term clinical outcomes of 2DRs versus 3DRs, data which will not be available from randomised clinical trials. Whilst many studies have shown 2DRs are non-inferior to 3DRs for short-term virologic and immunologic endpoints, data comparing clinical endpoints remains scarce (11–19,37,38).

There are some limitations to our analysis. We pre-specified the minimum number of participants on integrase inhibitors to be enrolled into RESPOND and therefore participants are not randomly selected. As this is an observational study, confounding by indication may affect our results, and whilst we have adjusted for a wide range of baseline characteristics, residual confounding cannot be excluded. Additionally, there is a relatively high proportion of missing data, for example for smoking status, and data completeness varies between cohorts. However, we performed several sensitivity

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analyses to handle missing data, all with similar results. Finally, the primary outcome of severe clinical outcome was analysed as a composite endpoint due to the low incidence of specific events, and 2DRs and 3DRs were analysed as groups. Specific regimens included in 2DRs and 3DRs were specified a priori and reflect real-world settings where individuals are treated with a range of regimens. The results may differ for specific events or for specific regimens.

There are, however, several important strengths to our analysis. To our knowledge, this is one of the first studies assessing clinical outcomes of 2DRs. RESPOND is a large and heterogeneous sample providing results which are generalisable to PLWH in Europe and Australia. Further, due to the size of the study, we were able to include a variety of 2DRs and assess relatively uncommon clinical endpoints.

In conclusion, after accounting for demographic and clinical characteristics, there was a similar incidence of severe clinical events on 2DRs and 3DRs. 2DRs appear to be a viable treatment option with regards to clinical outcomes in the first 2-3 years of exposure, although further research on resistance barriers and long-term durability of 2DRs is needed.

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Potential conflicts

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VV reports other from ViiV Healthcare, outside the submitted work; and I am a salaried employee of ViiV Healthcare and own GlaxoSmithKline stock.

FR reports other from Gilead Sciences, outside the submitted work; and I am a salaried employee of Gilead Sciences

JL reports personal fees from ViiV Healthcare, personal fees from Gilead Sciences, personal fees from Janssen Cilag, outside the submitted work;

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AVA reports that he represents the NGO EATG (European AIDS Treatment Group www.eatg.org) in the RESPOND steering Committee. The EATG received support funding from several drug companies (mainly Viiv, Gilead, MSD, Janssen). However I am certain that none of these fundings could have any influence in the submitted work. I am not a health professional but a member of my NGO, the EATG.

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Table 1. Characteristics of participants at regimen start

		Overall		Three-drug regimens		Two-drug regimens	
		N	(%)	n	(%)	n	(%)
Total		9791	(100)	8703	(88.9)	1088	(11.1)
Geographical region of Europe[1]	Western	4955	(50.6)	4537	(52.1)	418	(38.4)
	Southern	2261	(23.1)	1763	(20.3)	498	(45.8)
	Northern/ Australia	1679	(17.1)	1573	(18.1)	106	(9.7)
	Eastern	896	(9.2)	830	(9.5)	66	(6.1)
Gender	Male	7048	(72.0)	6253	(71.9)	795	(73.1)
	Female	2738	(28.0)	2445	(28.1)	293	(26.9)
	Transgender	3	(0.0)	3	(0.0)	0	(0.0)
Ethnicity	White	6976	(81.9)	6147	(81.5)	829	(84.9)
	Black	1125	(13.2)	1017	(13.5)	108	(11.1)
	Other	416	(4.9)	376	(5.0)	40	(4.1)
BMI	<18.5	363	(4.9)	310	(4.6)	53	(7.2)
	18.5-<25	4182	(56.0)	3752	(55.8)	430	(58.1)
	≥25	2923	(39.1)	2666	(39.6)	257	(34.7)
Smoking status	Never	2764	(40.9)	2505	(40.8)	259	(41.5)
	Current	2836	(41.9)	2599	(42.3)	237	(38.0)
	Previous	1162	(17.2)	1034	(16.8)	128	(20.5)
HIV Viral Load, copies/mL	< 200	8588	(87.7)	7648	(87.9)	940	(86.4)
	≥ 200	1203	(12.3)	1055	(12.1)	148	(13.6)
HIV risk	MSM	4037	(43.0)	3631	(43.5)	406	(39.6)
	IDU	1536	(16.4)	1343	(16.1)	193	(18.8)
	Heterosexual	3469	(37.0)	3076	(36.8)	393	(38.3)
	Other	337	(3.6)	303	(3.6)	34	(3.3)
Prior AIDS - non cancer		2021	(22.1)	1731	(21.2)	290	(29.1)
Prior ADC		440	(4.8)	379	(4.6)	61	(5.8)
HCV[2]		2568	(28.0)	2268	(27.9)	300	(29.0)
HBV[4]		488	(5.5)	445	(5.6)	43	(4.2)
Hypertension[5]		2620	(33.1)	2302	(32.0)	318	(44.5)
Diabetes[6]		711	(8.6)	604	(8.3)	107	(11.7)
Prior NADC		429	(4.7)	376	(4.6)	53	(5.1)

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Prior ESLD	87	(1.2)	72	(1.1)	15	(1.8)
Prior ESRD	52	(0.5)	35	(0.4)	17	(1.6)
Prior CVD[7]	362	(4.1)	285	(3.6)	77	(8.0)
Prior fracture	508	(6.6)	468	(6.7)	40	(6.2)
Prior CKD[8]	436	(4.9)	333	(4.2)	103	(10.6)
Prior CLEE[9]	3628	(38.7)	3247	(39.0)	381	(36.0)
Dyslipidaemia[10]	6587	(75.7)	5787	(74.7)	800	(83.9)
Any prior comorbidity	7257	(88.8)	6373	(87.9)	884	(95.6)
Continuous variables, median (IQR)						
Regimen start, mm/yy	07/15	(04/14, 08/16)	07/15	(03/14, 07/16)	12/15	(11/14, 01/17)
Age, years	48.3	(40.3, 54.9)	47.7	(39.7, 54.3)	52.6	(46.7, 59.0)
CD4 cell count nadir, cells/mm³†	202.0	(91.0, 309.0)	206.0	(96.0, 312.0)	170.0	(68.0, 280.0)
CD4 cell count at reg start, cells/mm³†	608.0	(423.0, 810.0)	605.0	(424.0, 809.0)	622.0	(408.6, 814.1)
CD8 cell count at reg start, cells/mm³†	790.0	(572.0, 1087.0)	786.0	(571.0, 1081.0)	827.0	(579.5, 1119.5)
Number of ARVs previously exposed to	6	(4,9)	6	(4,8)	8	(5,11)
Total previous treatment duration, months	9.9	(4.7,16.6)	9.5	(4.5,16.1)	14.3	(6.4,19.0)

Abbreviations: BMI-body mass index; VL-viral load; MSM-men who have sex with men; IDU-intravenous drug user; HCV – hepatitis C AB positive; HBV – hepatitis B surface antigenaemia; ADC-AIDS defining cancer; NADC-non-AIDS defining cancer; ESLD-end stage liver disease; ESRD-end stage renal disease; CVD-cardiovascular disease; CKD-chronic kidney disease; CLEE-chronic liver enzyme elevation; IQR-interquartile range; ARVs-antiretrovirals

Baseline is defined as the date of starting a regimen of interest

P-values for comparisons of 2DRs and 3DRs were all <0.05, except for gender (p=0.59), prior ESLD (0.09), CD4 cell count at regimen start (0.55) and CD8 cell count at regimen start (0.08).

[1]*Due to small numbers, Australia was combined with Northern Europe, and Eastern Central Europe combined with Eastern Europe.*

[2]*HCV was defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA-VL >615 IU/mL, and/or a positive genotype test* (26).

[4]*HBV was defined by a positive HBV surface antigen and/or HBV RNA-VL >357 IU/mL.*

[5]*Hypertension was confirmed by use of anti-hypertensives at any time before regimen start or if the most recent systolic or diastolic blood pressure measurement before regimen start was higher than 140 or 90 mmHg, respectively.*

[6]*Diabetes was defined by a reported diagnosis, use of anti-diabetic medication, glucose ≥11.1 mmol/L, and/or HbA1c ≥6.5% or ≥48 mmol/mol*

[7]*CVD was defined using a composite diagnosis of myocardial infarction, stroke or invasive cardiovascular procedure.*

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[8]*CKD was confirmed if there were two consecutive measurements of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 measured at least 3 months apart. eGFR was calculated using the CKD-EPI creatinine equation* (39)

[9]*Chronic liver enzyme elevation was confirmed if there were two consecutive measurements of ALT >50 IU/L for males or >35 IU/L for females, measured between 6 months and 2 years apart. One normal ALT measurement was allowed between elevated measurements.*

[10]*Dyslipidaemia was defined as total cholesterol>239.4mg/dL or HDL cholesterol<34.7mg/dL or triglyceride >203.55mg/dL or use of lipid lowering treatments* (40)

[†]*CD4 and CD8 cell count were taken as the most recent measurements in the 12 months prior to regimen start. If no measurements were taken prior to starting the regimen, the first measurement within 12 weeks after regimen start was used, and CD4 cell nadir was recorded as the same as CD4 cell count at regimen start.*

**Denominator for percentages is all participants with non-missing data.*

Total unknown n (%): Ethnicity 1274 (13.0), BMI 2323 (23.7), Smoking status 3029 (30.9), HIV risk 412 (4.2), prior AIDS-non cancer 636 (6.5), prior AIDS cancer 570 (5.8), HCV 623 (6.4), HBV 896 (9.2), hypertension 1880 (19.2), diabetes 1565 (16.0), prior NADC 570 (5.8), prior ESLD 2288 (23.4), prior ESRD 721 (7.4), prior CVD 866 (8.8), prior fracture 2135 (21.8), prior CKD 857 (8.8), prior CLEE 405 (4.1), dyslipidaemia 1086 (11.1), prior comorbidity 1616 (16.5).

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Table 2. Comparison of the incidence of individual severe clinical events between two and three drug regimens

				Univariable			Multivariable*		
			N events	IRR	(95% CI)	P	IRR	(95% CI)	P
Death	Regimen Type	3DR	186	1			1		
		2DR	18	0.90	(0.55, 1.46)	0.66	0.69	(0.42, 1.12)	0.13
NADC	Regimen Type	3DR	130	1			1		
		2DR	26	1.86	(1.22, 2.84)	0.004	1.35	(0.88, 2.09)	0.17
CVD	Regimen Type	3DR	109	1			1		
		2DR	14	1.19	(0.68, 2.08)	0.54	0.80	(0.45, 1.41)	0.44
AIDS – non cancer	Regimen Type	3DR	80	1			1		
		2DR	11	1.28	(0.68, 2.40)	0.44	1.27	(0.67, 2.43)	0.47

Abbreviations: IRR-incidence rate ratio; CI-confidence interval; NADC-non-AIDS defining cancer; CVD-cardiovascular disease; 3DR-three-drug regimen; 2DR-two-drug regimen

**Multivariable model adjusted for age, CD4 cell count at regimen start, smoking status, number of drugs previously exposed to*

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Figure legends

Figure 1. Study flow chart

Abbreviations: ART-antiretroviral therapy; INSTI-integrase inhibitor; ARV-antiretroviral; 2DR-two-drug regimen; 3DR-three-drug regimen; VL-viral load; DTG-dolutegravir; RPV-rilpivirine; RAL-raltegravir; DRV/b-boosted darunavir; NVP-nevirapine; ATV-atazanavir; ATV/b-boosted ATV; ETV-etravirine; 3TC-lamivudine

**More than one reason can apply*

†3DRs consisted of 2 nucleoside reverse transcriptase inhibitors plus the 3rd drug listed. 3DRs were chosen so the 3rd drug include the same ARVs listed in the 2DRs

Figure 2. Crude incidence rate/1000 person years of follow-up and 95% CI for two drug regimens versus three drug regimens

Abbreviations: NADC-non-AIDS defining cancer; CVD-cardiovascular disease; ESLD-end stage liver disease; ESRD-end stage renal disease; 3DR-three-drug regimen; 2DR-two-drug regimen; PYFU-person years of follow-up

Figure 3. Incidence rate ratio comparing events on two drug regimens vs three drug regimens

Abbreviations: IRR-incidence rate ratio; 2DR-two-drug regimen; 3DR-three-drug regimen.

All events and validated events - adjusted analyses adjusted for age, gender, ethnicity, BMI, smoking status, HIV risk group, HIV viral load at regimen start, nadir CD4 count, CD4 cell count at regimen start, viral hepatitis C, viral hepatitis B, prior hypertension, prior diabetes, prior AIDS defining event (excluding cancer), prior AIDS cancer, prior non-AIDS cancer, prior end stage liver disease, prior cardiovascular disease, prior fracture, prior chronic kidney disease, prior dyslipidaemia, number of drugs previously exposed to

Recommended regimens - adjusted analysis adjusted for age, gender, ethnicity, smoking status,CD4 cell count at regimen start, viral hepatitis C, prior AIDS defining event (excluding cancer), prior non-AIDS cancer, prior cardiovascular disease, prior chronic kidney disease, number of drugs previously exposed to

Recommended regimens included-2DRs: dolutegravir (DTG) plus rilpivirine (RPV), DTG plus lamivudine (3TC), boosted atazanavir (ATV/b) plus 3TC, darunavir (DRV) plus 3TC, DRV plus RPV; 3DRs: DTG or RPV or ATV/b or DRV plus 2 nucleoside reverse transcriptase inhibitors

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Figure 1

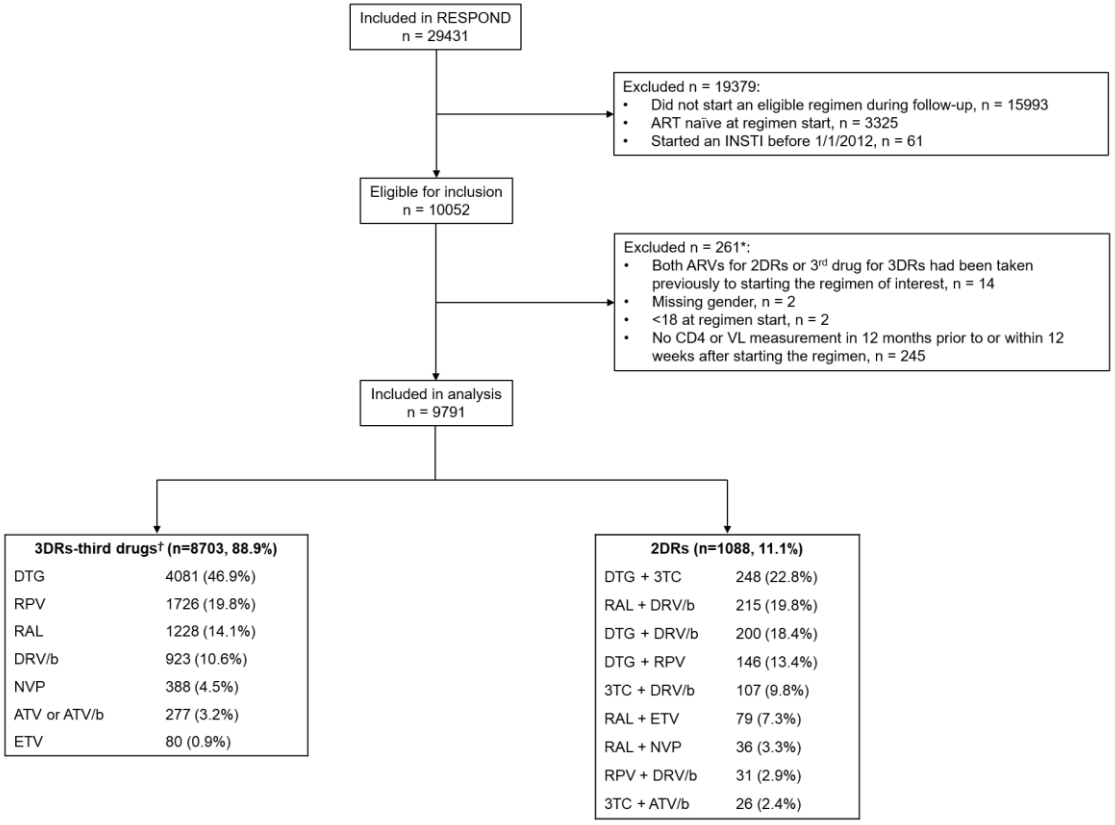

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Figure 2

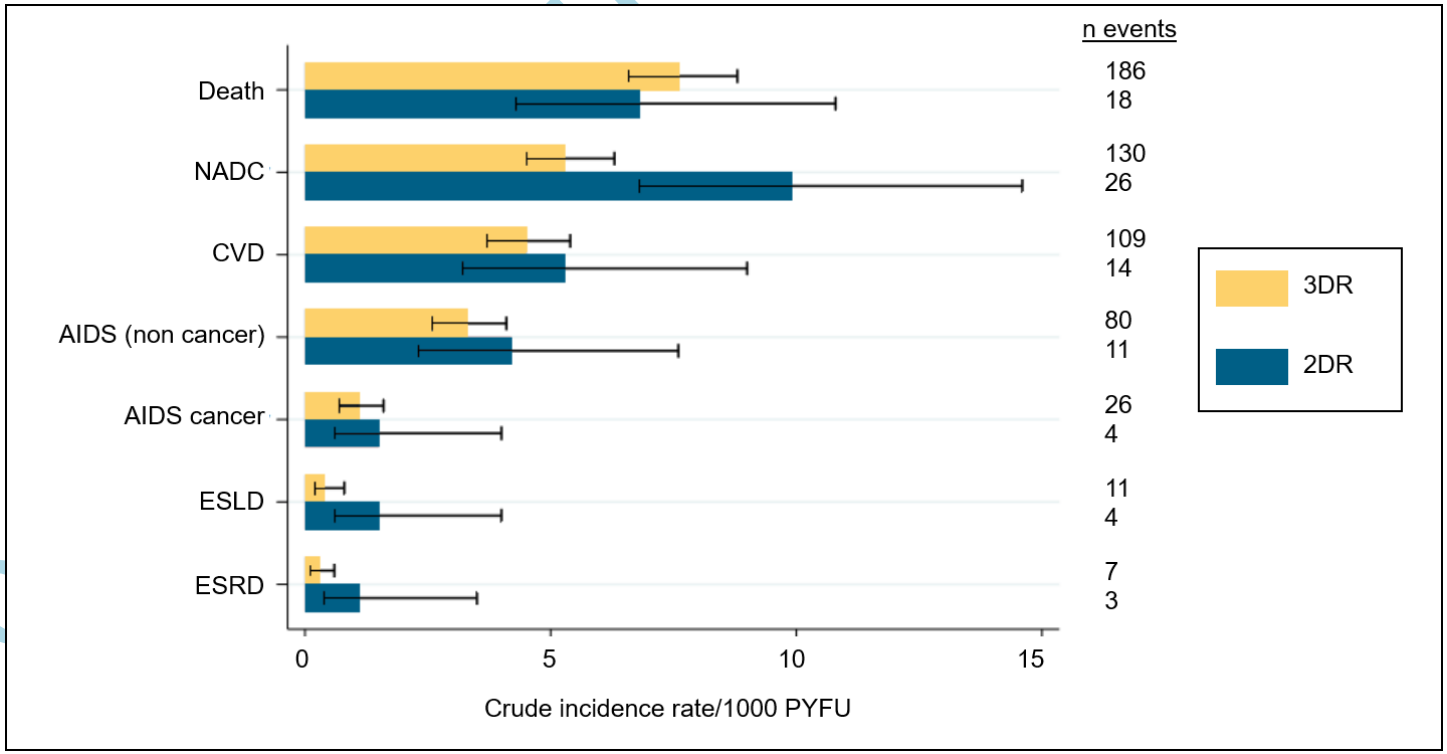

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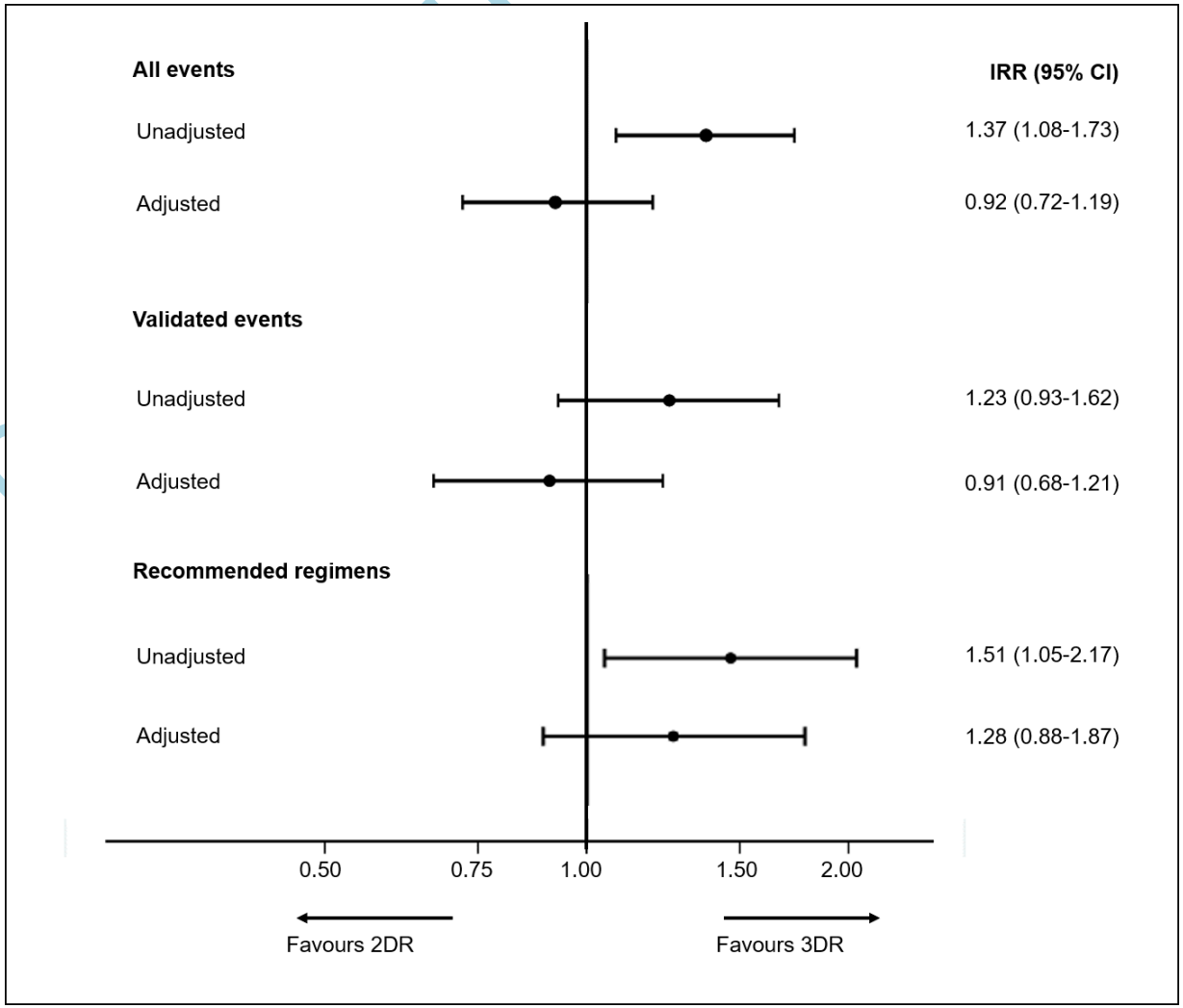
Figure 3



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