CROI 2020

CLINICAL OUTCOMES OF TWO DRUG REGIMENS (2DRs) VS. THREE DRUG REGIMENS (3DRs) IN HIV

Poster No. 0487

L. Greenberg[1], L. Ryom[2], B. Neesgaard[2], G. Wandeler[3], T. Staub[3], M. Gisinger[4], M. Skoll[5], H. Günthard[6], A. Scherrer[6], C. Mussini[7], C. Smith[8], M. Johnson[8], S. De Wit[9], C. Necsoi[9], C. Pradier[10], F. Wit[11], C. Lehmann[12], A. d'Arminio Monforte[13], J.M. Miró[14], A. Castagna[15], V. Spagnuolo[15], A. Sönnerborg[16], M. Law[17], J. Hutchinson[17], N. Chkhartishvili[18], N. Bolokadze[18], J-C. Wasmuth[19], C. Stephan[20], V. Vannappagari[21], F. Rogatto[22], J. Llibre[23], C. Duvivier[24], J. Hoy[17], M. Bloch[17], H.C. Bucher[6], A. Calmy[25], A. Volny Anne[26] A. Pelchen-Matthews[1], J.D. Lundgren[2], L. Peters[2], L. Bansi-Matharu[1], A. Mocroft[1] *on behalf of the RESPOND study group*

[1]Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, UK; [2]CHIP, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Denmark; [3]EuroSIDA Cohort, CHIP, Rigshospitalet, RegionH, Denmark; [4]Medizinische Universität Innsbruck, Austria; [5]Wiener Medizinische Universität, Austria; [6]Swiss HIV Cohort Study (SHCS), University of Zurich & University Hospital Basel, Switzerland; [7]Modena HIV Cohort, Università degli Studi di Modena, Italy; [8]The Royal Free HIV Cohort Study, Royal Free Hospital, University College London, United Kingdom; [9]Saint Pierre University Hospital, Université Libre de Bruxelles, Belgium; [10]Nice HIV Cohort, Université Côte d'Azur et Centre Hospitalier Universitaire, Nice, France; [11]AIDS Therapy Evaluation in the Netherlands Cohort (ATHENA), Stichting HIV Monitoring (SHM), Netherlands; [12]University Hospital Cologne, Cologne, Germany; [13]Italian Cohort Naive Antiretrovirals (ICONA), ASST Santi Paolo e Carlo, Italy; [14]Hospital Clinic-IDIBAPS. University of Barcelona, Barcelona, Spain; [15]Direttore Scuola di Specializzazione in Malattie Infettive e Tropicali Università Vita-Salute San Raffaele, Italy; [16]Division of Infectious Diseases, Karolinska Institutet and Department of Infectious Diseases, Karolinska University Hospital; [17]The Australian HIV Observational Database (AHOD), UNSW, Australia; [18]Georgian National AIDS Health Information System (AIDS HIS), Infectious Diseases, AIDS and Clinical Immunology Research Center, Georgia; [19]University Hospital Bonn, Germany; [20]Frankfurt HIV Cohort Study, Johann Wolfgang Goethe-University Hospital, Germany; [21]ViiV Healthcare, RTP, USA; [22]Gilead science, Foster City, USA; [23]Hospital Universitari Germans Trias i Pujol · Department of Internal Medicine, HIV Unit; [24]APHP-Hôpital Necker-Enfants Malades, Service de Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, IHU Imagine, Paris, France ; [25]HIV/AIDS Unit in Geneva University Hospital; [26] European AIDS Treatment Group

Lauren Greenberg
Institute for Global Health,
Rowland Hill St,
London, UK, NW3 2PF
Tel: 0208 016 8051
Email: l.greenberg@ucl.ac.uk

BACKGROUND

- Several clinical trials and small observational studies have shown good short term virological efficacy and tolerability of 2DRs (1-6)
- Reasons for switching to 2DRs are multifactorial and include concerns about long-term toxicities and drug-drug interactions (7-8)
- Little is known from large studies regarding clinical outcomes of 2DRs

METHODS

- Antiretroviral treatment experienced participants in the RESPOND consortium starting an eligible regimen during follow-up (FU) were included (Table 1)
- Baseline was defined as date of starting the first regimen of interest after cohort enrolment or 1/1/2012, whichever occurred the latest
- If a participant started a 2DR and 3DR of interest, they were included in the 2DR group
- Reasons for discontinuing the previous regimen were compared. Reasons were only counted if the previous regimen was discontinued ≤7 days before starting an eligible regimen
- This analysis focused on severe clinical events including: AIDS (cancer and non-cancer), non-AIDS defining cancer (NADC), cardiovascular disease (CVD; invasive cardiovascular procedures, myocardial infarction, or stroke), end stage liver disease (ESLD), end stage renal disease (ESRD), and death
- Individuals were followed until the first severe event of any type or until last clinical visit or 1/10/2018, whichever occurred first
- Incidence rates (IR) of clinical events between those starting a 2DR vs. 3DR were compared using Poisson regression with adjustment for baseline characteristics
- Sensitivity analyses were performed including centrally validated events only and only including approved 2DRs

Table 1: Number of individuals on each treatment regimen

3DR			2DR		
Regimen	**n**	**(%)**	**Regimen**	**n**	**(%)**
Total	8703	(88.9)	Total	1088	(11.1)
2 NRTIs + DTG	4081	(46.9)	DTG + 3TC*	248	(22.8)
2 NRTIs + RPV	1726	(19.8)	RAL + DRV/b	215	(19.8)
2 NRTIs + RAL	1228	(14.1)	DTG + DRV/b	200	(18.4)
2 NRTIs + DRV/b	923	(10.6)	DTG + RPV*	146	(13.4)
2 NRTIs + NVP	388	(4.5)	3TC + DRV/b	107	(9.8)
2 NRTIs + ATV or ATV/b	277	(3.2)	RAL + ETV	79	(7.3)
2 NRTIs + ETV	80	(0.9)	RAL + NVP	36	(3.3)
			RPV + DRV/b	31	(2.9)
			3TC + ATV/b	26	(2.4)

Abbreviations: NRTI – nucleoside reverse transcriptase inhibitor; 3TC – lamivudine; ATV – atazanavir; DRV – darunavir; DTG – dolutegravir; ETV – etravirine; RAL – raltegravir; RPV – rilpivirine; NVP – nevirapine; /b – boosted with cobicistat or ritonavir; Eligible 3DRs were chosen so that the 3rd antiretrovirals were the same antiretrovirals as used in the 2DRs; *approved 2DRs

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RESULTS

- Overall, 9791 individuals were included; 1088 (11.1%) on 2DRs and 8703 (88.9%) on 3DRs
- Individuals on 2DRs were older and a higher proportion had a prior AIDS defining event or prevalent comorbidity (Table 2)
- The most common 2DRs were DTG plus 3TC (22.8%) and RAL plus DRV/b (19.8%) (Table 1)
- The most common 3DR was 2 NRTIs plus DTG (46.9%). The most common NRTI backbones were TDF plus FTC (45.0%) and ABC plus 3TC (40.5%)
- The main reason for discontinuing the previous regimen before starting a 2DR or 3DR was toxicity (30.9% 2DRs vs 31.1% 3DRs; p=0.87); renal toxicity was most common for switches to 2DRs (37.9%) and toxicity from the nervous system was most common for switches to 3DRs (28.3%)

Table 2: Baseline clinical characteristics

		All		3DR		2DR	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
		9791	(100)	8703	(88.9)	1088	(11.1)
Gender	Male	7048	(72.0)	6253	(71.9)	795	(73.1)
Ethnicity	White	6976	(71.2)	6147	(70.6)	829	(76.2)
BMI (kg/m^2)	<18.5	363	(3.7)	310	(3.6)	53	(4.9)
	≥25	2923	(29.9)	2666	(30.6)	257	(23.6)
Current smoking		2836	(29.0)	2599	(29.9)	237	(21.8)
Risk of acquisition	MSM	4037	(41.2)	3631	(41.7)	406	(37.3)
HIV VL	<200 Cp/mL	8588	(87.7)	7648	(87.9)	940	(86.4)
Viral hepatitis B	Positive	488	(5.0)	445	(5.1)	43	(4.0)
Viral hepatitis C	Positive	2568	(26.2)	2268	(26.1)	300	(27.6)
AIDS defining event	Yes	2021	(20.6)	1731	(19.9)	290	(26.7)
Comorbidity	Yes	7321	(74.8)	6433	(73.9)	888	(81.6)
		Median	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**
Regimen start date (mm/yy)		08/15	(05/14, 09/16)	07/15	(04/14, 08/16)	12/15	(12/14, 01/17)
Age (years)		48	(40, 55)	48	(40, 54)	53	(47, 59)
CD4 count (cells/μL)		608	(423, 810)	605	(424, 809)	622	(409, 814)
Number of previous antiretrovirals exposed to		6	(4-9)	6	(4-8)	8	(5-11)

Percentage of unknown variable (all): Ethnicity 13.0; BMI 23.7; Smoking 30.9; Risk of acquisition 4.2; Hepatitis B 9.2; Hepatitis C 6.4; AIDS defining event 5.8;Comorbidity 16.3. Comorbidities included: diabetes, hypertension, non AIDS defining cancer, cardiovascular disease, chronic kidney disease, end stage liver disease, end stage renal disease, fracture, dyslipidaemia. Differences between 3DRs and 2DRs are significant (p≤0.05), except for gender, hepatitis C, and CD4 count

- Median FU was 2.6 (IQR 1.4-3.8) years and was similar on 2DRs and 3DRs (2.2 (1.2-3.2) on 2DRs and 2.7 (1.4-3.8) on 3DRs)
- Overall, there were 619 clinical events during 27159 person years of FU [PYFU] (IR/1000 PYFU [95% CI] 23.3 [21.6-25.2])
- The most common events were death (IR 7.5/1000 PYFU [6.5-8.6]), and NADC (IR 5.8/1000 PYFU [4.9-6.8]) (Figure 1)
- There were 79 events on 2DRs during 2642 PYFU (IR 30.9 [24.8-38.5]) and 540 events on 3DRs during 24516 PYFU (IR 22.5/1000 PYFU [20.7-24.5])
- In unadjusted analyses, there was a higher IR of events on 2DRs (IR ratio 1.37 [1.08-1.73], p=0.009). However, after adjustment for potential confounders (age and number of drugs previously exposed to in particular) there was no significant difference between 2DRs and 3DRs (IR ratio 0.92 [0.72-1.19], p=0.53) (Figure 2)
- Sensitivity analyses including only centrally validated events and only including approved 2DRs showed similar results

Figure 1: Crude IR/1000 PYFU and 95% CI for 2DR vs 3DR

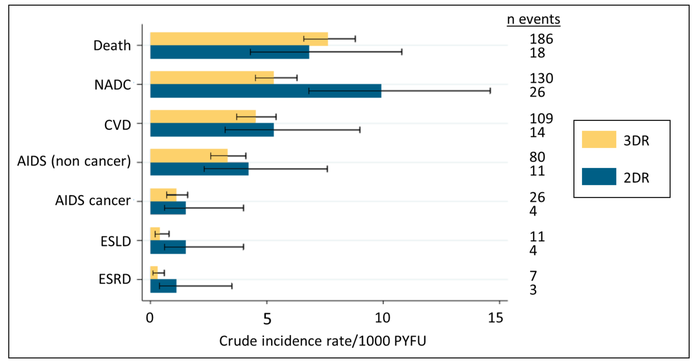
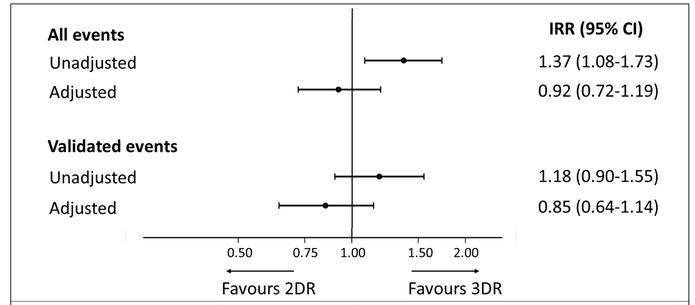


Figure 2: Incidence rate ratio comparing events on 2DR vs 3DR



Adjusted analyses adjusted for age, gender, ethnic origin, BMI, smoking status, HIV risk group, HIV viral load at regimen start, CD4 cell nadir, 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, prior treatment duration

LIMITATIONS

- Residual confounding cannot be ruled out
- This analysis focuses on a composite endpoint, rather than individual events
- Due to limited numbers, we were unable to include treatment naïve individuals in the analysis

CONCLUSIONS

- This is the first large, international cohort to assess rigorously defined severe clinical outcomes on 2DRs
- After accounting for demographic and clinical characteristics, there was a similar incidence of events on 2DRs and 3DRs
- 2DRs appear to be a viable treatment option with regards to clinical outcomes. Further research on long-term durability of 2DRs is needed

The RESPOND Study Group: https://www.chip.dk/Studies/RESPOND/Study-Group

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