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Uptake and Effectiveness of Two-drug Compared to Three-drug Antiretroviral Regimens among HIV-positive Individuals in Europe

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BACKGROUND

Although two-drug antiretroviral regimens (2DR) have been assessed in several randomized controlled trials, there is little information on uptake and outcomes of these regimens in routine clinical practice[1]. We investigated the use of 2DR in the EuroSIDA cohort[2].

METHODS

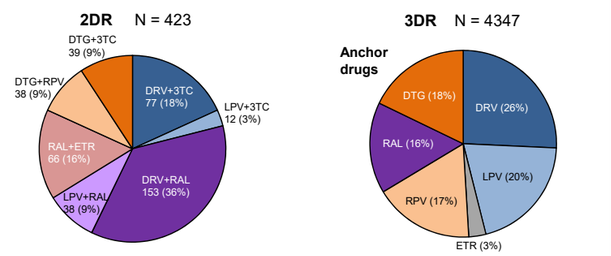
- Study population: Individuals who started a 2DR containing darunavir/r, lopinavir/r, raltegravir, dolutegravir, rilpivirine or etravirine, and those who started a 3-drug regimen (3DR) with one of these antiretrovirals (ARVs), between 1/7/2010 and 31/12/2016.
- Virological response was defined using the FDA snapshot algorithm at 6 or 12 months after starting the ARV regimen (treatment failure: viral load (VL) ≥400 copies/ml or no VL at 6 or 12 months ±16 weeks, change of ARV regimen, AIDS or death).
- Immunological response was defined as a 100 cell/µl increase or as a 25% increase in CD4 count at 12 months ±16 weeks.

RESULTS

1. Characterisation of ART regimens used

423 individuals started a 2DR after 01 July 2010, and 4347 started a 3DR consisting of two NRTIs and an anchor drug. The regimens used are summarised in **Figure 1**.

Figure 1. Characterisation of the ART regimens used



Protease Inhibitors: DRV, darunavir; LPV, lopinavir.
Non-nucleoside RT inibitors: ETR, etravirine; RPV, rilpivirine.
Integrase inhibitors; DTG, dolutegravir; RAL, raltegravir;
Nucleotide/nucleoside RT inhibitor: lamivudine (3TC)

The most common nucleotide/nucleoside RT inhibitors were: tenofovir disoproxil fumarate (TDF): 58%; emtricitabine (FTC): 54%; 3TC, 43%; and abacavir (ABC): 34%.

2. Uptake of 2DR

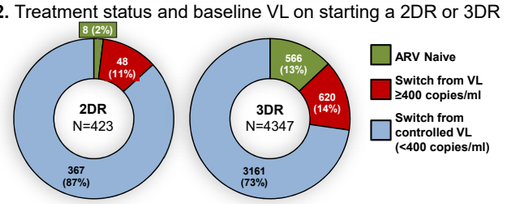
Characteristics of individuals on 2DR or 3DR are shown in Table 1. Compared to those starting a 3DR, those on 2DR tended to be older, have higher CD4 counts and controlled VL, and were more treatment-experienced, with higher cumulative exposure to all the main ARV classes. Only 8 individuals starting a 2DR (2%) were ARV-naive; most switched to the 2DR with controlled VL (**Figure 2**). Individuals on 2DR also had higher levels of comorbidities and clinical conditions (**Table 1**).

Table 1. Baseline characteristics of individuals starting a 2DR or 3DR after 30th June 2010.

	2DR		3DR		
	N	(%)	N	(%)	P- value
	423		4347		
Age (years) *	52.1	(46.2, 57.6)	46.4	(37.8, 53.1)	<0.0001
Gender - Male	314	(74)	3081	(71)	0.1458
Ethnic Group - White	368	(87)	3767	(87)	0.8441
Region of Europe ** - South	195	(46)	1059	(24)	<0.0001
West/Central	131	(31)	1146	(26)	
North	55	(13)	776	(18)	
East	42	(10)	1366	(31)	
Mode of infection - MSM	164	(39)	1590	(37)	0.6241
Intravenous drug user	105	(25)	1159	(27)	
Heterosexual contact	117	(28)	1262	(29)	
Baseline CD4 (cells/µl) *	552	(381, 788)	536	(341, 743)	0.0321
CD4 nadir (cells/µl) *	190	(96, 319)	226	(120, 347)	0.001
Baseline Viral Load - <400 copies/ml	370	(87)	3235	(74)	<0.0001
Years on ART *	17.0	(12.1, 19.8)	11.5	(5.8, 16.6)	<0.0001
Clinical conditions					
Prior AIDS	140	(33)	1052	(24)	<0.0001
Co-infection with HCV	161	(38)	1800	(41)	0.0006
Hypertension	247	(58)	2081	(48)	<0.0001
Dyslipidaemia	334	(79)	2594	(60)	<0.0001
Diabetes	46	(10.9)	211	(4.9)	<0.0001
Cardiovascular Disease	31	(7.3)	171	(3.9)	0.0009
Non-AIDS defining Malignancies	28	(6.6)	148	(3.4)	0.0008
Chronic Kidney Disease	41	(9.7)	139	(3.2)	<0.0001

* Median and inter-quartile range.
** Region of Europe included South (Greece, Italy, Portugal and Spain as well as Israel and Argentina), West/Central (Austria, Belgium, France, Germany, Luxembourg and Switzerland), North (Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom) and Eastern Europe (Belarus, Bosnia-Herzegovina, Bulgaria, Croatia, the Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, the Russian Federation, Serbia, Slovakia, Slovenia and the Ukraine).
MSM, men who have sex with men.

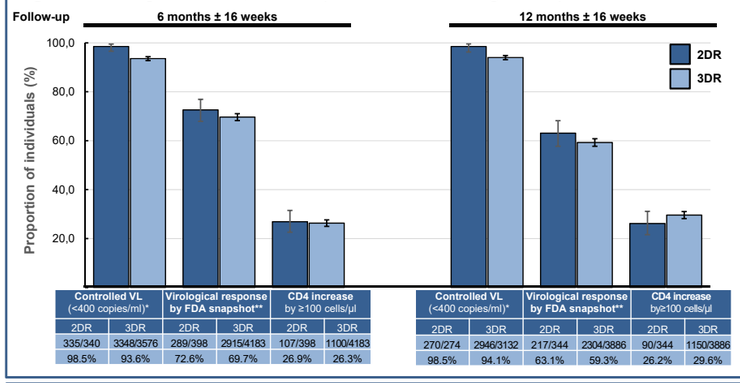
Figure 2. Treatment status and baseline VL on starting a 2DR or 3DR



3. Effectiveness of 2DR

Outcomes were assessed in individuals with 6 or 12 months follow-up available. More than 93% of individuals with data available had a controlled VL 6 or 12 months after starting their 2DR or 3DR. Virological responses by the FDA snapshot and immunological responses (increases in CD4 T cell numbers) were similar for 2DR and 3DR (**Figure 3**) and logistic regression modelling showed similar odds of a virological or immunological response for individuals on 2DR and 3DR (**Figure 4**).

Figure 3. Virological control, FDA snapshot and immunological responses 6 or 12 months after starting a 2DR or 3DR



Controlled VL (<400 copies/ml)*		Virological response by FDA snapshot**		CD4 increase by ≥100 cells/µl	
2DR	3DR	2DR	3DR	2DR	3DR
335/340	3348/3576	289/398	2915/4183	107/398	1100/4183
98.5%	93.6%	72.6%	69.7%	26.9%	26.3%

Controlled VL (<400 copies/ml)*		Virological response by FDA snapshot**		CD4 increase by≥100 cells/µl	
2DR	3DR	2DR	3DR	2DR	3DR
270/274	2946/3132	217/344	2304/3886	90/344	1150/3886
98.5%	94.1%	63.1%	59.3%	26.2%	29.6%

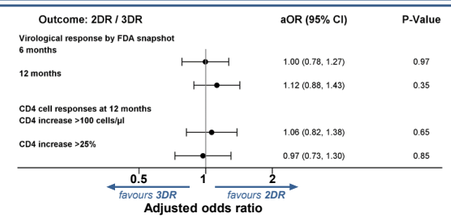
Bars show 95% confidence intervals (CI) of proportions.

* of those with a VL measurement available at 6 months (10 and 42 weeks) or 12 months (36 – 68 weeks)

**** FDA snapshot failures**:
6 months – Among individuals on 2DR, 5 individuals had a VL >400 copies/ml, 58 had no VL in the time window, 51 stopped the 2DR, and there was 1 death and 1 new AIDS diagnosis; while for 3DR, 228 individuals had a VL >400 copies/ml, 607 had no VL in the time window, 548 changed ARVs, and there were 27 deaths and 24 new AIDS diagnoses.
12 months – Among individuals on 2DR, 5 individuals had a VL >400 copies/ml, 69 had no VL in the time window, 72 stopped the 2DR, and there were 2 deaths and 1 new AIDS diagnosis; while for 3DR, 188 individuals had a VL >400 copies/ml, 752 had no VL in the time window, 860 changed ARVs, and there were 45 deaths and 30 new AIDS diagnoses.

Figure 4. Adjusted odds ratios for virological or CD4 cell responses for 2DR compared to 3DR

ORs were adjusted for age group (<50 or ≥50 years), gender, race (Caucasian vs. other), region of Europe (South, Central, North or East), HIV risk group (MSM, intravenous drug user, heterosexual contact or other), recent HIV diagnosis (prior 2 years), baseline CD4 cell counts (<200, 200-350, 350-500 or ≥500 cells/µl), baseline VL (<400 or ≥400 RNA copies/ml), prior ART (vs. treatment naïve), liver-related events and chronic kidney disease.



CONCLUSIONS

2DR were largely used by individuals with well-controlled viremia and high CD4 counts who tended to be older and have more comorbidities. Virological and immunological outcomes were in line with results from clinical trials and suggest immunological and virological responses to 2DR were similar to 3DR, although confounding by indication cannot be excluded.

References

1. Achhra AC, Mwasakifwa G, Amin J, Boyd MA. **Efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy: a systematic review and meta-analysis.** *Lancet HIV* 2016; 3(8):e351-e360.
2. See: https://chip.dk/Studies/EuroSIDA

The EuroSIDA Study Group: https://chip.dk/Studies/EuroSIDA
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