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

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Lancet Januar 2018

Journal Club 12. März 2018

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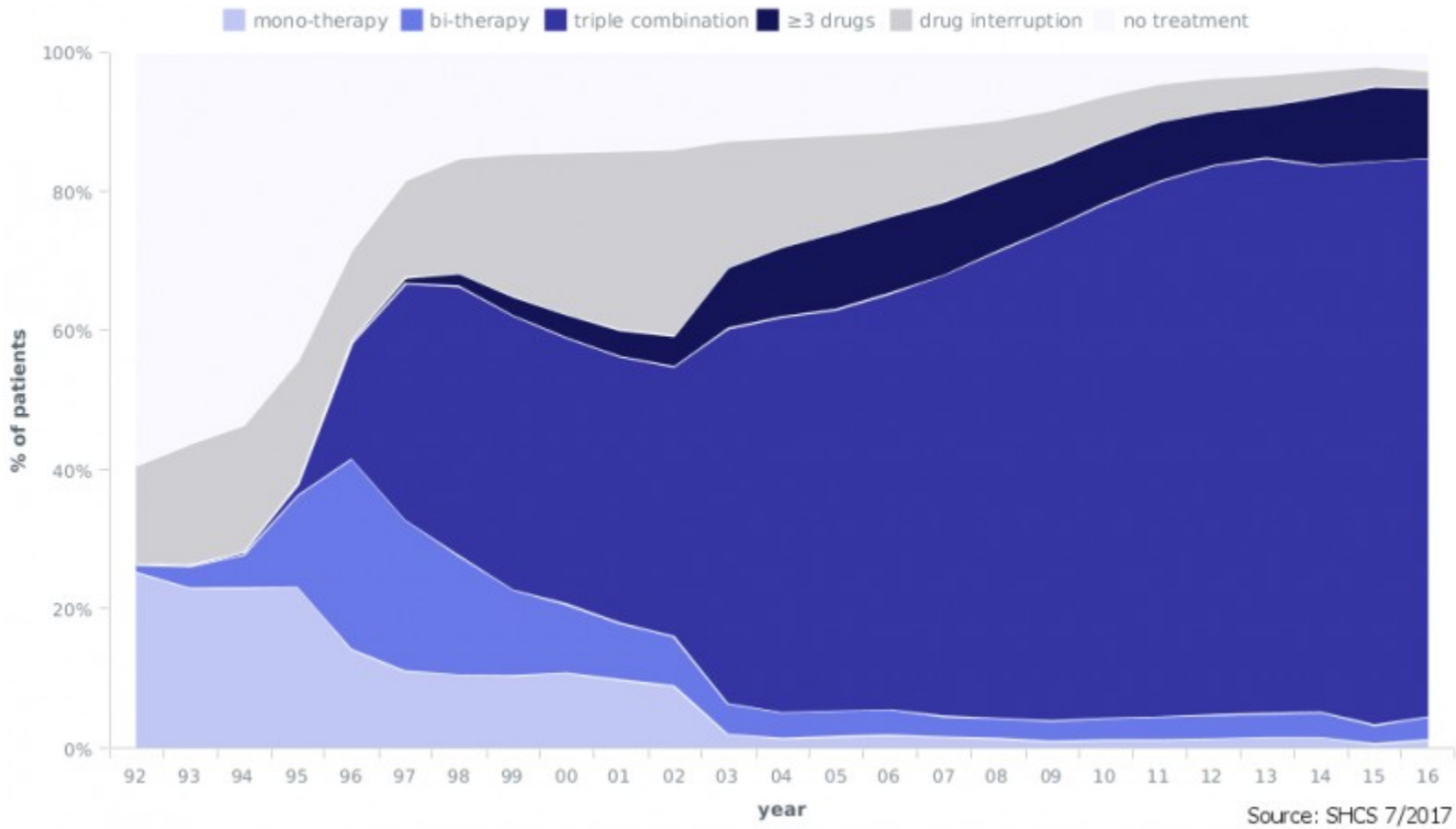
Hintergrund

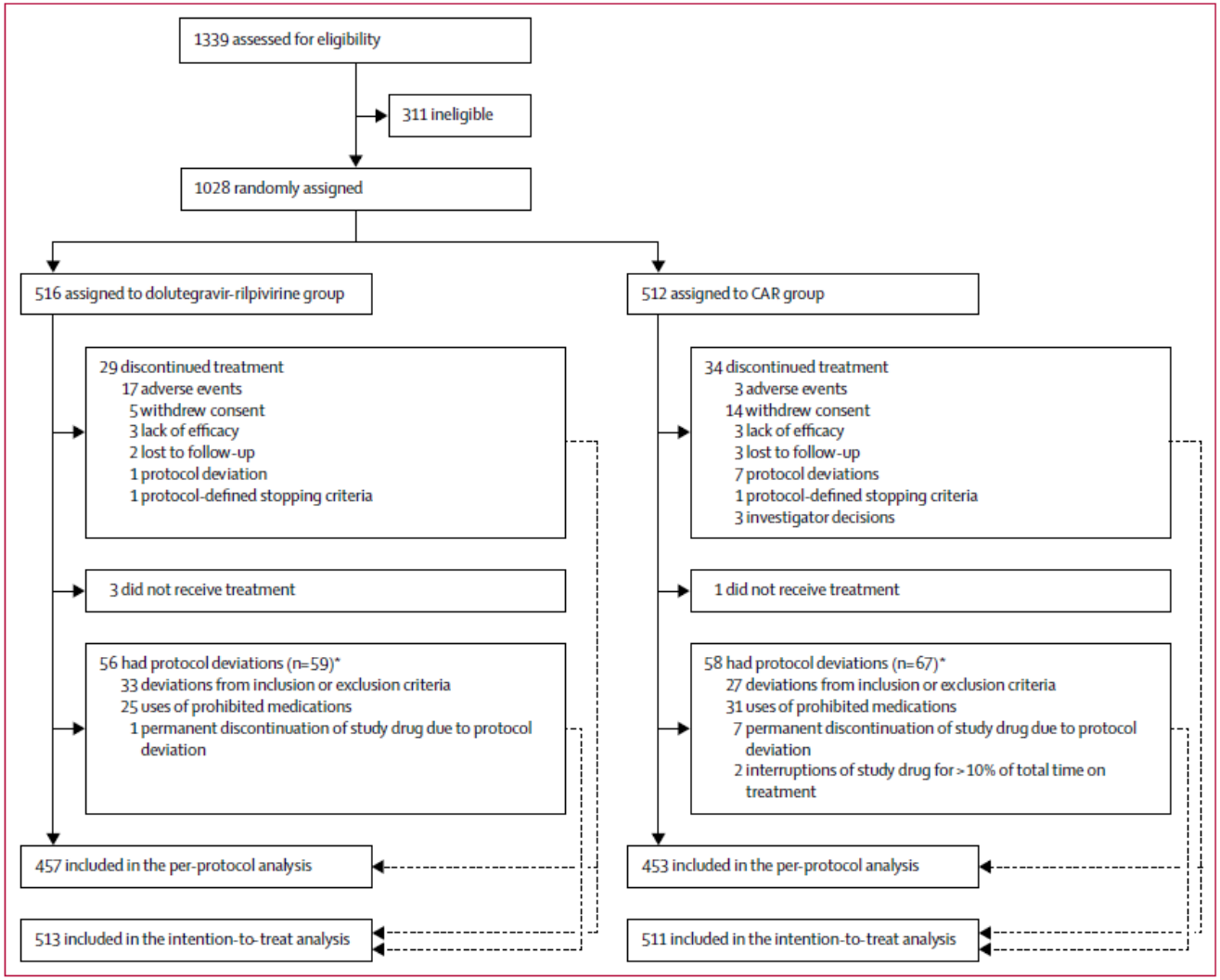


NRTI
NNRTI
PI
INSTI

Studiendesign und Methode

- Open-label, parallel-group, multicentre, randomized, non-inferiority, insgesamt 148 Wochen
- Einschlusskriterien: >18 Jahre, supprimiert >6 Monate (<50 Kopien/ml), 1. oder 2. ART-Regime
- Ausschlusskriterien: Major-resistance (PI, INSTI, NRTI, NNRTI), bisheriges virologisches Versagen, Hepatitis B, geplante Hepatitis C-Therapie, Suizidalität, (…)
- 1:1 Randomisierung nach 3. Wirkstoff (PI, INSTI, NNRTI), Alter und Teilnahme in Knochendichte-Substudie
- Primärer Endpunkt: Viral load <50 Kopien/ml bei Woche 48
- Sekundäre Endpunkte: snapshop efficacy bei Woche 24 und 48 und in vordefinitierten Subgruppen bei Woche 48 (3. Wirkstoff), CD4-Zellzahl, adverse events, Laborveränderungen, neu aufgetretene Resistenzen

Trial profile: SWORD-1 und SWORD-2

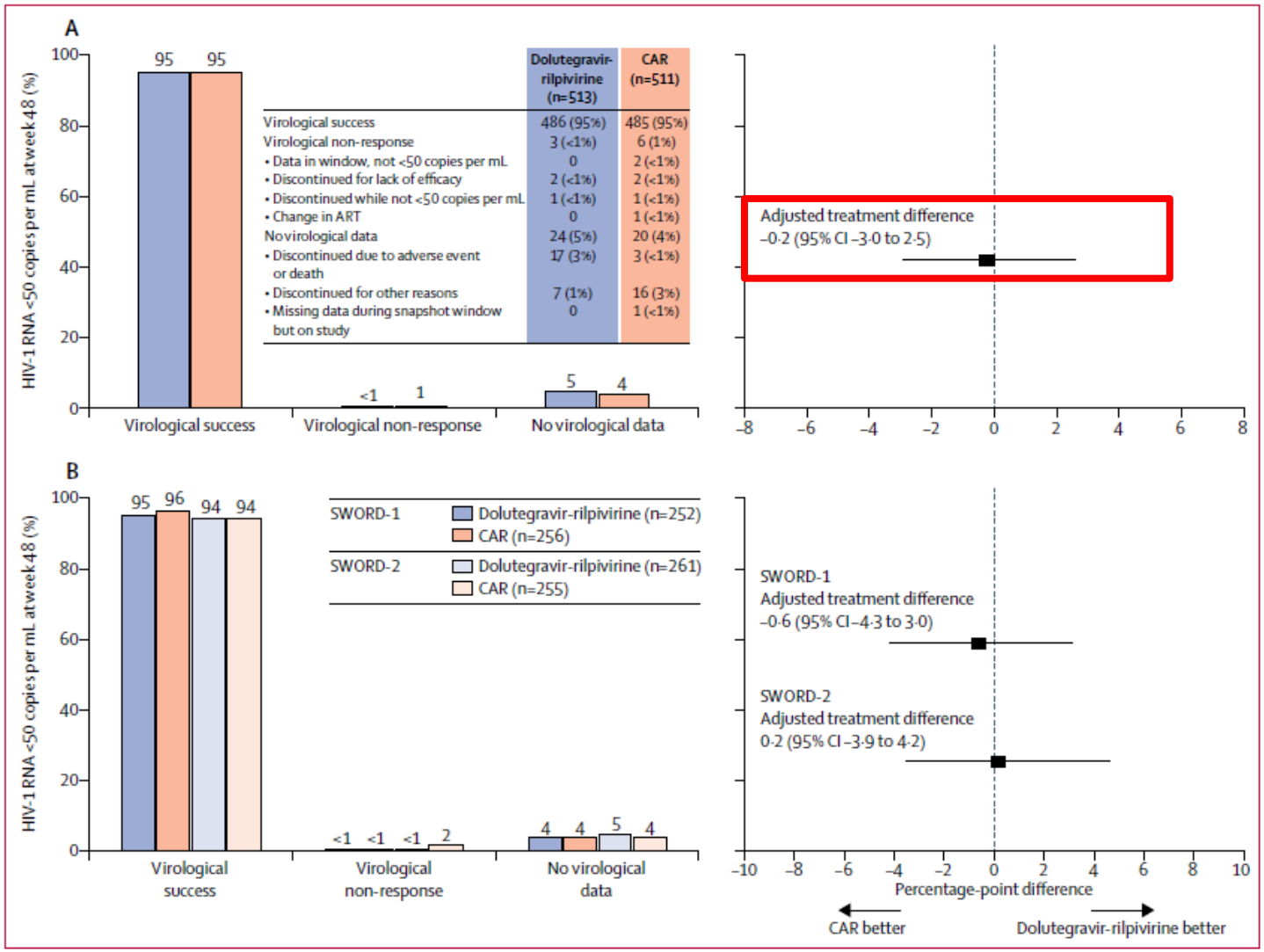


Baseline-Charakteristika

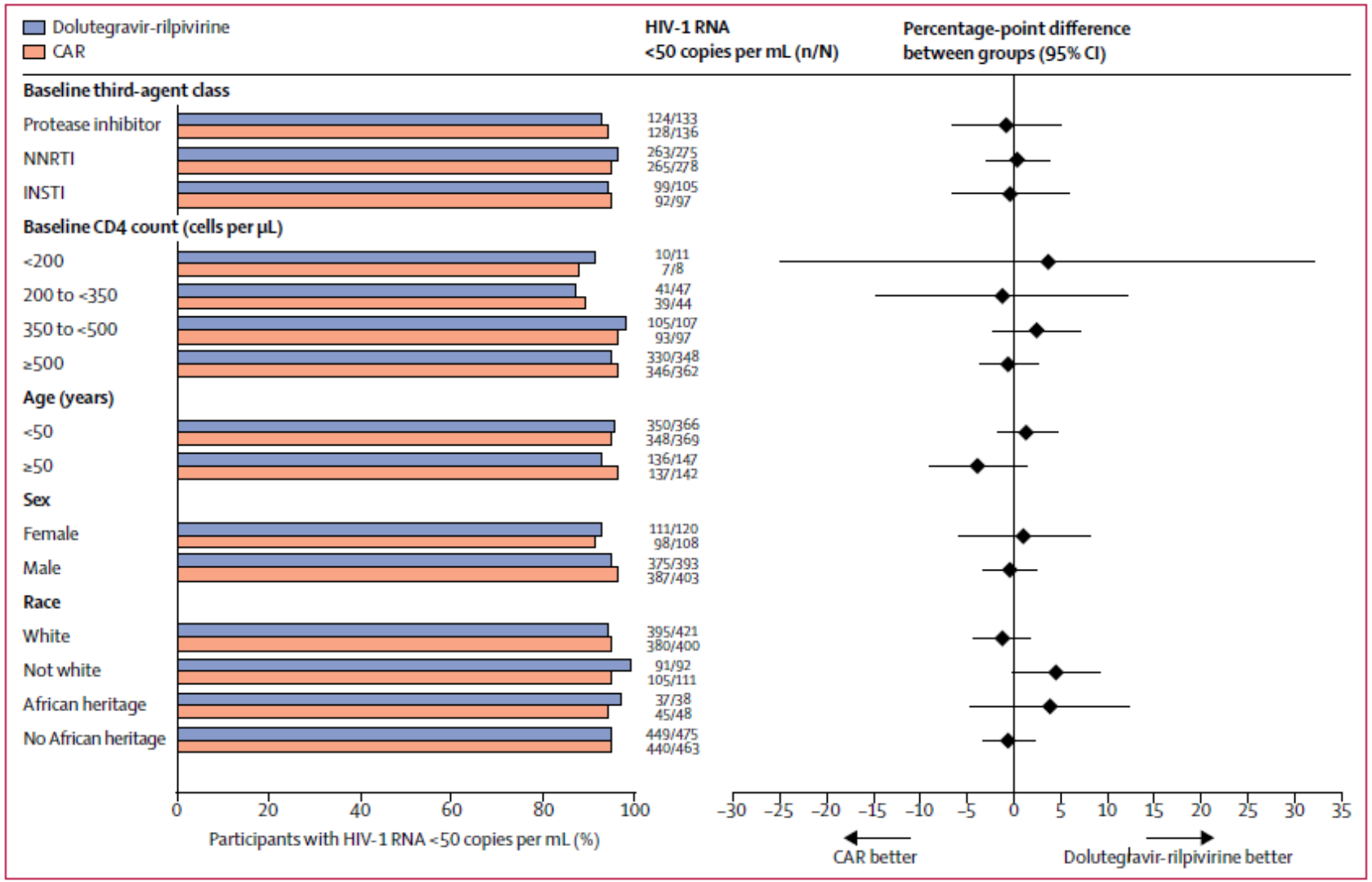
- 80% Weiss
- ¾ Männer
- ¾ <50 Jahre

	Dolutegravir-rilpivirine group (n=513)	CAR group (n=511)
Age (years)	43 (21–79)	43 (22–76)
<50	366 (71%)	369 (72%)
≥50	147 (29%)	142 (28%)
Sex		
Female	120 (23%)	108 (21%)
Male	393 (77%)	403 (79%)
Ethnicity		
Hispanic or Latino	67 (13%)	82 (16%)
Not Hispanic or Latino	446 (87%)	429 (84%)
Race		
American Indian or Alaska Native	14 (3%)	14 (3%)
Asian	38 (7%)	50 (10%)
Black or African American	37 (7%)	47 (9%)
Native Hawaiian or other Pacific Islander	2 (<1%)	0
White	421 (82%)	398 (78%)
Mixed race	1 (<1%)	2 (<1%)
Baseline CD4 count (cells per µL)	611 (3–1774)	638 (9–1671)
CDC category		
A (asymptomatic, lymphadenopathy, or acute HIV)	400 (78%)	385 (75%)
B (symptomatic, not AIDS)	55 (11%)	68 (13%)
C (AIDS)	58 (11%)	57 (11%)
Missing	0	1 (<1%)
Time since first ART until day 1 (months)	51 (8–221)	53 (9–270)
Baseline ART third-agent class		
NNRTI*	275 (54%)	278 (54%)
Protease inhibitor†	133 (26%)	136 (27%)
INSTI‡	105 (20%)	97 (19%)
Most common ART at screening§		
Tenofovir disoproxil fumarate	374 (73%)	359 (70%)
Emtricitabine	352 (69%)	341 (67%)

Virologisches Outcome (1)



Virologisches Outcome (2)



Veränderungen laborchemischer Parameter

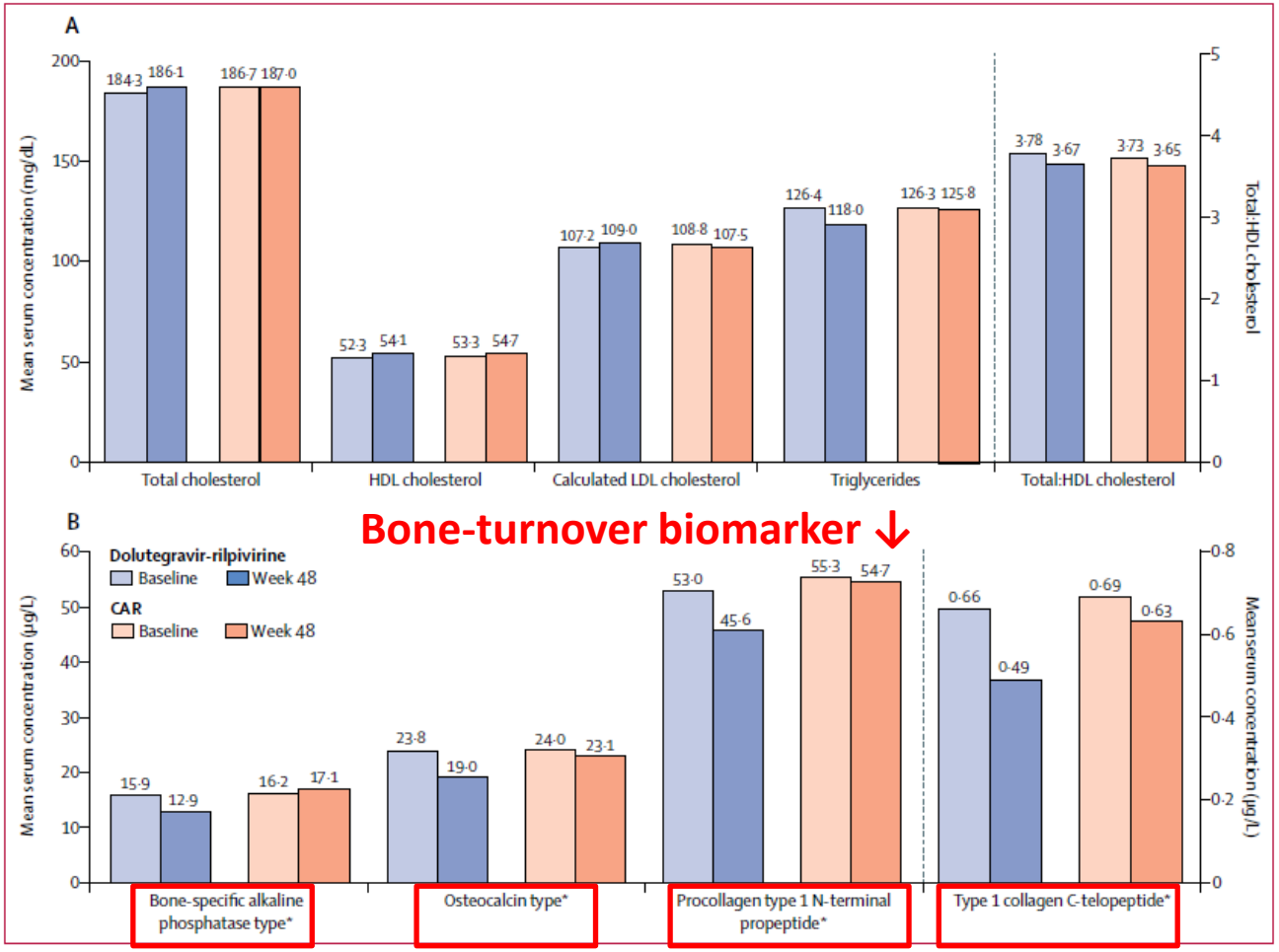
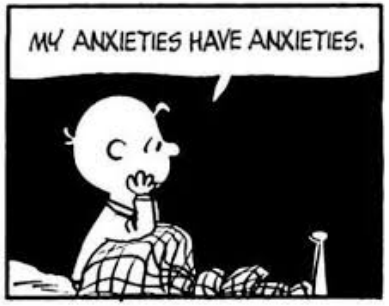


Figure 4: **Serum concentrations of lipids (A) and bone-turnover biomarkers (B) in the pooled SWORD-1 and SWORD-2 intention-to-treat study population**
CAR=current antiretroviral regimen. *p<0·0001 from an analysis of covariance model for comparisons between dolutegravir-rilpivirine and CAR in change from baseline at week 48 for each bone-turnover biomarker (in logarithmic scale) adjusted for baseline third-agent class, age, sex, body-mass index, smoking status, and baseline bone-turnover biomarker concentration.

Adverse Events

Any adverse event: vergleichbar
Drug-related: 19 vs. 2%
Adverse events leading to withdrawal: 3 vs. 1%



	Dolutegravir-rilpivirine group (n=513)	CAR group (n=511)
Any adverse events*	395 (77%)	364 (71%)
Psychiatric disorders†	61 (12%)	32 (6%)
Nasopharyngitis	49 (10%)	50 (10%)
Headache	41 (8%)	23 (5%)
Upper respiratory tract infection	24 (5%)	37 (7%)
Diarrhoea	32 (6%)	27 (5%)
Back pain	15 (3%)	31 (6%)
Bronchitis	23 (4%)	15 (3%)
Influenza	14 (3%)	17 (3%)
Arthralgia	21 (4%)	9 (2%)
Drug-related adverse events*	97 (19%)	9 (2%)
Headache	11 (2%)	0
Diarrhoea	8 (2%)	1 (<1%)
Serious adverse events	27 (5%)	21 (4%)
Drug-related	4 (1%)	1 (<1%)
Fatal‡	1 (<1%)	1 (<1%)
Adverse events by grade		
Grade 1	247 (48%)	244 (48%)
Grade 2	116 (23%)	100 (20%)
Grade 3	27 (5%)	17 (3%)
Grade 4	5 (1%)	3 (1%)
Adverse events leading to withdrawal from the study§	17 (3%)	3 (1%)
Psychiatric disorders	7 (1%)	1 (<1%)
Gastrointestinal disorders	7 (1%)	0
Neoplasms (benign, malignant, or unspecified)	2 (<1%)	2 (<1%)
Nervous system disorders	1 (<1%)	0
Hepatobiliary disorders	1 (<1%)	0
Respiratory, thoracic, or mediastinal disorders	1 (<1%)	0

Diskussion

- Studie: nicht verblindet, high income countries, junge Population
- Lebenslange Therapie notwendig
  - → Reduktion der (Langzeit-) Nebenwirkungen sinnvoll (Studie über insgesamt 148 Wochen geplant und Substudie zur Knochendichte)
  - → Reduktion der Interaktionen mit anderen Medikamenten bei zunehmend älteren und kränkeren HIV-Infizierten
- Zweierkombination Dolutegravir + Rilpivirin (Juluca©) seit November 2017 FDA zugelassen (ca. $ 2’700)
- Weitere mögliche Kombinationen für duale Therapien: 3TC+Dolutegravir, Cabotegravir+RPV, … ?
- Entscheidung über Therapieregime weiterhin individuell