Viral Suppression Rates in Salvage Treatment With Raltegravir Improved With the Administration of Genotypic Partially Active or Inactive Nucleoside/Tide Reverse Transcriptase Inhibitors

Alexandra U. Scherrer, MSc, Viktor von Wyl, PhD,* Jürg Böni, DVM,† Sabine Yerly, MSc,‡ Thomas Klimkait, PhD,§ Philippe Bürgisser, PhD,‖ Christian Garzoni, MD,¶ Bernard Hirschel, MD,# Matthias Cavassini, MD,** Manuel Battegay, MD,†† Pietro L. Vernazza, MD,‡‡ Enos Bernasconi, MD,§§ Bruno Ledergerber, PhD,* Huldrych F. Günthard, MD* and the Swiss HIV Cohort Study (SHCS)*

Background: Nucleoside reverse transcriptase inhibitors (NRTIs) are often administered in salvage therapy even if genotypic resistance tests (GRTs) indicate high-level resistance, but little is known about the benefit of these additional NRTIs.

Methods: The effect of <2 compared with 2 NRTIs on viral suppression (HIV-1 RNA < 50 copies/mL) at week 24 was studied in salvage patients receiving raltegravir. Intent-to-treat and per-protocol analyses were performed; last observation carried forward imputation was used to deal with missing information. Logistic regressions were weighted to create a pseudopopulation in which the probability of receiving <2 and 2 NRTIs was unrelated to baseline factors predicting treatment response.

Results: One-hundred thirty patients were included, of whom 58.5% (n = 76) received <2 NRTIs. NRTIs were often replaced by other drug classes. Patients with 2 NRTIs received less additional drug classes compared with patients with <2 NRTIs [median (IQR): 1 (1–2) compared with 2 (1–2), *P* Wilcoxon < 0.001]. The activity of non-NRTI treatment components was lower in the 2 NRTIs group compared with the <2 NRTIs group [median (IQR) genotypic sensitivity score: 2 (1.5–2.5) compared with 2.5 (2–3), *P* Wilcoxon < 0.001]. The administration of <2 NRTIs was associated with a worse viral suppression rate at week 24. The odds ratios were 0.34 (95% confidence interval: 0.13 to 0.89, *P* = 0.027) and 0.19 (95% confidence interval: 0.05 to 0.79, *P* = 0.023) when performing the last observation carried forward and the per-protocol approach, respectively.

Conclusions: Our findings showed that partially active or inactive NRTIs contribute to treatment response, and thus the use of 2 NRTIs in salvage regimens that include raltegravir seems warranted.

Key Words: HIV-1, nucleoside reverse transcriptase inhibitor, raltegravir, salvage treatment

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INTRODUCTION

The treatment options for patients infected with highly drug-resistant HIV markedly improved with the introduction of new antiretroviral compounds, such as fusion inhibitors, second-generation nonnucleoside reverse transcriptase inhibitors (NNRTIs), or new boosted protease inhibitors (PIs), CCR5 antagonists, and integrase inhibitors.[1–7] To date, knowledge about the optimal combination of these compounds

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From the *Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zürich, University of Zürich, Zürich, Switzerland; †Institute of Medical Virology, Swiss National Center for Retroviruses, University of Zürich, Zürich, Switzerland; ‡Central Laboratory of Virology, Geneva University Hospital, Geneva, Switzerland; §Institute for Medical Microbiology, University of Basel, Basel, Switzerland; ‖Division of Immunology and Allergy, University Hospital Lausanne, Lausanne, Switzerland; ¶Division of Infectious Diseases, University Hospital Berne, Bern, Switzerland; #Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland; **Infectious Diseases Service, University Hospital Lausanne, Lausanne, Switzerland; ††Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland; ‡‡Division of Infectious Diseases, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; and §§Regional Hospital Lugano, Lugano, Switzerland.

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The members of the SHCS are listed in Appendix I.

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Correspondence to: Alexandra U. Scherrer, MSc, Division of Infectious Diseases and Hospital Epidemiology, Rämistrasse 100, CH-8091 Zürich, Switzerland (e-mail: alexandra.scherrer@usz.ch).

in salvage therapy is lacking. Nucleoside reverse transcriptase inhibitors (NRTIs) are often co-administered in salvage therapy, even if genotypic resistance tests (GRTs) indicate high-level resistance. A therapeutic benefit is assumed because of the possible residual activity of these NRTIs and the maintenance of a resistant virus with reduced replicative capacity.[8–12] On the other hand, costs, drug–drug interactions, tolerability, and toxicity of these additional NRTIs have to be taken into account. NRTIs can cause mitochondrial dysfunction by inhibiting the DNA γ-polymerase resulting in plasma hyperlactataemia and variable clinical syndromes, such as lipoathrophy and peripheral neuropathy.[13–21]

The clinical benefit of NRTIs with decreased activity due to drug resistance mutations to date has not been properly assessed. The number of antiretroviral compounds has increased, and additional drug classes have become available, making NRTIs potentially expendable in salvage therapy.

Here, we focused on salvage regimens including raltegravir (RAL) because this drug is now frequently used in Switzerland to treat patients with highly resistant viruses.[22] Using data from the highly representative Swiss HIV Cohort Study (SHCS),[23,24] we report on the genotypic activity and composition of salvage therapies with RAL and the effect of partially active or inactive NRTIs on the viral suppression rate.

METHODS

Data and Patient Selection

Data from the SHCS were included for our analysis (up to June 30, 2010). The SHCS is a nationwide clinic-based cohort study with continuous enrolment and at least semi-annual study visits (www.shcs.ch).[24] It has been approved by ethical committees of all participating institutions, and written informed consent has been obtained from participants. The SHCS drug resistance database contains all HIV resistance tests performed by the 4 authorized laboratories in Switzerland using commercial assays (Viroseq Vs. 1 PE Biosystems, Rotkreuz, Switzerland; Virsoseq Vs. 2, Abbott AG, Baar, Switzerland; vircoTYPE HIV-1 Assay, Virco Lab, Mechelen, Belgium) and in-house methods.[25] Sequences are stored in SmartGene's (Zug, Switzerland) Integrated Database Network System version 3.5.8).[26]

Study Population

To analyze the effect of partially active or inactive NRTIs in salvage therapy, the SHCS was screened for patients who started a regimen containing RAL. Inclusion criteria were a GRTs on antiretroviral therapy (ART) before the RAL start and baseline HIV-1 RNA >500 copies per milliliter. Patients receiving more than 2 NRTIs were excluded from the study due to the small number of cases (n = 12). For further analyses, patients receiving 0 or 1 NRTI were considered as one group and compared with patients receiving 2 NRTIs beside RAL. This classification turned out to be appropriate because patients treated with 0 and 1 NRTI had similar characteristics, and results did not differ markedly when analyzing these 2 groups separately (not shown).

Baseline Characteristics and Estimated Activity of Available Treatment Options

Patient characteristics were compared between patients receiving <2 NRTIs and 2 NRTIs with Fisher exact test (categorical variables) and Wilcoxon rank-sum test (continuous variables). The baseline was set at the date of RAL start. The self-reported adherence was categorized in 2 groups: patients who never missed a drug and patients who missed ≥1 drug in the 4 weeks preceding the study visit.[27] To assess the availability of active antiretroviral compounds, results from Stanford interpretation algorithm (version 6.0.8) were mapped to a genotypic sensitivity score (GSS) for all approved drugs except enfuvirtide (T20), maraviroc (MAR), and RAL. The 5 resistance categories from the Stanford algorithm were regrouped as follows: viruses with a GSS less than 15 were considered as fully susceptible (GSS = 1), those with a GSS between 15 and 59 were considered to have intermediate resistance (GSS = 0.5), and those with a GSS greater than 59 were considered to be fully resistant (GSS = 0). If T20 and MAR have not previously been included in a failing regimen, they were considered fully susceptible because transmission of HIV with resistance to T20 is very rare and coreceptor tropism testing was always performed before MAR prescription (Trofile assay, Monogram Biosciences, San Francisco, CA).[28]

Virological Outcome

The effect of NRTIs in salvage therapies with RAL was assessed at week 24. The viral suppression rate (HIV-1 RNA < 50 copies/mL) was analyzed, and different approaches were implemented as follows: an intent-to-treat analysis was performed with 2 different methods dealing with missing information, last observation carried forward (LOCF) and missing equal failure (m = f), and a per-protocol analysis. For the per-protocol analysis, only patients who did not change, stop, or interrupt treatment until week 24 and who had a viral load measurement between week 18 and week 30 were included.

Logistic regressions were performed and adjusted for ethnicity, age, sex, the GSS of the treatment (without NRTIs), number of drug classes, HIV-1 RNA, and CD4 cell count before RAL treatment start. In the present study, confounding by indication must be addressed because many factors, for example, number of drug classes in the background regimen, GSS of available drugs, or adherence, may influence not only the suppression rate but also the number of NRTIs physicians chose for the salvage therapy. A solution to overcome a selection bias is to perform a marginal structural model.[29,30] Weights were defined as the inverse of the probability for receiving <2 NRTIs as estimated by multivariable logistic regression including the following possible confounders: sex, adherence, age, transmission category, ethnicity, MAR, etravirine (ETV), or darunavir (DRV) in the background treatment, GSS of available NRTIs, GSS of PIs, and NNRTIs in the salvage therapy, CD4 nadir, baseline HIV-1 RNA, year of treatment, and whether the patient was ever treated with mono/dual NRTI therapy. This method creates a pseudopopulation, in which the probability for receiving <2 or 2 NRTIs is unrelated to baseline factors which are also prognostic for the

treatment response. Multicollinearity was checked, and a variance inflation factor <3 was tolerated for regression models. To check whether single observations had a disproportionately large impact on our results due to the weighting, the analysis was repeated 1000 times on bootstrapped data sets.

To confirm results, an additional analysis was performed assessing time to viral suppression with a Cox regression model. The same covariables were included as in the logistic regression described above, and the same procedure was followed to calculate the weights. Patients were included when they had at least 1 HIV-1 RNA measured, and they were censored when they changed, stopped, or interrupted therapy.

Statistical analyses were performed with Stata 11 SE (StataCorp, College Station, TX), all confidence intervals (CIs) are 95% CI, and the level of significance was set at $P = 0.05$.

RESULTS

Study Population and Baseline Characteristics

A total of 142 patients who had a viral load >500 copies per milliliter, a GRT performed before RAL treatment start, and follow-up HIV-1 RNA measurements were considered for analysis. Patients who received more than 2 NRTIs were excluded from further analysis (11 with 3 NRTIS, 1 with 4 NRTIs). Patients who received no NRTI (n = 38, 26.8%) or 1 NRTI (n = 38, 26.8%) were handled as one group and compared with patients receiving 2 NRTIs (n = 54, 38.0%).

Most baseline characteristics were similar between patients with <2 NRTIs and 2 NRTIs (Table 1), but patients with 2 NRTIs were younger, had more often baseline HIV-1 RNA >100,000 copies per milliliter and tended to have started the first ART later. The self-reported adherence during the 4 weeks proceeding the study visit before RAL start was

TABLE 1. Baseline Characteristics of Patients Who Started Salvage Treatment With Raltegravir

	<2 NRTIs (n = 76)*	2 NRTIs (n = 54)*	P*
Sociodemographic factors			
Median (IQR) age (in yrs)	49 (42.5–51)	43 (40–48)	0.009
Sex			
Female	28.9% (19.1–40.5)	25.9% (15.0–39.6)	0.704
Male	71.0% (59.5–80.9)	74.1% (60.4–85.0)	
Ethnicity			
White	82.9% (72.5–90.6)	87.0% (75.1–94.6)	0.519
Other	17.1% (9.4–27.5)	13.0% (5.4–24.9)	
Transmission category			
MSM	51.3% (39.6–63.0)	55.6% (41.4–69.1)	0.972
HET	28.9% (19.1–40.5)	25.9% (15.0–39.6)	
IDU	15.8% (8.4–26.0)	14.8% (6.6–27.1)	
Other	4.0% (0.8–11.1)	3.7% (0.5–12.8)	
Immunological and virological factors			
Baseline HIV-1 RNA (copies/mL)			
500–9999	43.4% (32.1–55.3)	37.0% (24.3–51.3)	0.068
10,000–99,999	44.7% (33.3–56.6)	35.2% (22.7–49.4)	
≥100,000	11.8% (5.6–21.3)	27.8% (16.5–41.6)	
Median (IQR) CD4 (cells/μL)	226 (128.5–302.5)	256 (94–314)	0.962
Median (IQR) CD4 nadir (cells/μL)	71.5 (18.5–176)	82 (33–172)	0.498
Subtype			
B	80.3% (69.5–88.5)	87.0% (75.1–94.6)	0.310
Other	19.7% (11.5–30.5)	13.0% (5.4–24.9)	
CDC stage			
A	23.7% (14.7–34.8)	18.5% (9.3–31.4)	0.702
B	38.2% (27.3–50.0)	44.4% (30.9–58.6)	
C	38.2% (27.3–50.0)	37.0% (24.3–51.3)	
Treatment history			
Median (IQR) year of therapy start	1995 (1993–1996)	1996 (1994–1998)	0.037
Ever mono/dual NRTI therapy	88.2% (78.7–94.4)	79.6% (66.5–89.4)	0.184
Prior DRV	2.6% (0.3–9.2)	9.3% (3.1–20.3)	0.099
Prior ETV	5.3% (1.5–12.9)	3.7% (0.5–12.8)	0.676
Prior MAR	2.6% (0.3–9.2)	0.0% (0.0–6.6)	0.230
Prior T20	18.4% (10.4–29.0)	18.5% (9.3–31.4)	0.989

*Percentage (95% confidence interval) or median (IQR), *P* value based on Fisher exact test (categorical variables) or Wilcoxon rank-sum test.
MSM, men who have sex with men.

similar: 72.2% (2 NRTIs group) and 71.1% (<2 NRTIs group). Additional factors that might be a sign of non-adherence were tested as follows: the number of therapies patients started, the number of treatment interruptions (cessation of ART and resumption at a later date), psychiatric treatment in the past, alcohol abuse, and current intravenous drug use or smoking. All these characteristics were similar among groups (data not shown).

The median number of NRTI, NNRTI, and PI mutations (International AIDS Society [IAS-USA] drug resistance mutations printed in bold)[31] was comparable between patients with <2 and 2 NRTIs, 9 [interquartile range (IQR): 5–13] and 10 (7–14.5) ($P = 0.100$), respectively. Of note, the median number of NRTI mutations was lower in the 2 NRTIs group, 4 (1–5) compared with 5 (3–5) in the <2 NRTIs group ($P = 0.040$). The number of major PI and NNRTI mutations was not significantly different.

Available Treatment Options Based on Genotypic Data

Some treatment options differed between patients with 2 and <2 NRTIs and were important reasons to perform a weighted logistic regression. The GSS of the best 2 NRTIs was <1, 1, and >1 in 29.6%, 20.4%, and 50.0% of patients with 2 NRTIs, slightly higher than in the <2 NRTIs group (43.4%, 26.3%, and 30.3%, $P = 0.075$). As shown in Table 2, the NRTI with the highest estimated activity was tenofovir (TDF), with only 3.7% (2 NRTIs group) and 11.8% (<2 NRTIs group) being fully resistant. In contrast, full resistance against the following NRTI groups was common in patients with 2 and <2 NRTIs: zidovudine/stavudine (37.0% and 59.2%), emtricitabine (FTC)/lamivudine (3TC) (81.5 and 85.5%), and abacavir (ABC)/didanosine (DDI) (37.0% and 52.6%). Resistance against the new NNRTI ETV was rare 1.9% (2 NRTIs group) and 5.3% (<2 NRTI group). In contrast, full resistance against first-line NNRTIs (EFV and NVP) was common in patients with 2 and <2 NRTIs, 63.0% and 68.4%, respectively. DRV was the best PI with an estimated full activity in 73.9% of the cases, followed by tipranavir (48.5%), lopinavir (43.9%), saquinavir (39.2%), and indinavir (38.5%).

TABLE 2. Genotypic Activity of Potential Antiretroviral Compounds for Salvage Treatment

Estimated Activity*	<2 NRTIs, Percentage (95% CI)	2 NRTIs, Percentage (95% CI)	P
GSS of NRTIs			
ZDV/D4T			
1	23.7% (14.7–34.8)	33.3% (21.1–47.5)	0.041
0.5	17.1% (9.4–27.5)	29.6% (18.0–43.6)	
0	59.2% (47.3–70.3)	37.0% (24.3–51.3)	
FTC/3TC			
1	6.6% (2.2–14.7)	14.8% (6.6–27.1)	0.212
0.5	7.9% (3.0–16.4)	3.7% (0.5–12.8)	
0	85.5% (75.6–92.5)	81.5% (68.6–90.8)	
ABC/DDI			
1	9.2% (3.8–18.1)	35.2% (22.7–49.4)	0.001
0.5	38.2% (27.3–50.0)	27.8% (16.5–41.6)	
0	52.6% (40.8–64.2)	37.0% (24.3–51.3)	
TDF			
1	18.4% (10.4–29.0)	42.6% (29.2–56.8)	0.006
0.5	69.7% (58.1–79.8)	53.7% (39.6–67.4)	
0	11.8% (5.6–21.3)	3.7% (0.5–12.8)	
GSS of NNRTIs			
EFV/NVP			
1	28.9% (19.1–40.5)	35.2% (22.7–49.4)	0.735
0.5	2.6% (0.3–9.2)	1.9% (0.1–9.9)	
0	68.4% (56.8–78.6)	63.0% (48.7–75.7)	
ETV			
1	50.0% (38.3–61.7)	61.1% (46.9–74.1)	0.347
0.5	44.7% (33.3–56.6)	37.0% (24.3–51.3)	
0	5.3% (1.5–12.9)	1.9% (0.1–9.9)	
GSS of PIs			
Highest scoring PI			
1	73.7% (62.3–83.1)	79.6% (66.5–89.4)	0.423
0.5	23.7% (14.7–34.8)	20.4% (10.6–33.5)	
0	2.6% (0.3–9.2)	0.0% (0.0–6.6)	

*A GSS of 1 denotes full susceptibility, 0.5 intermediate resistance and 0 full resistance. GSS was calculated with Stanford algorithm version 6.0.8.
D4T, stavudine; ZDV, zidovudine.

Composition of the Salvage Therapy With RAL

The composition of the non-NRTI treatment patients received together with RAL differed markedly between groups. The number of non-NRTI drugs beside RAL was lower in the 2 NRTIs group. The percentage of patients with ≤1, 2, and 3 drugs was 68.5%, 27.8%, and 3.7% compared with 30.3%, 56.6%, and 13.2% ($P < 0.001$). Also the number of drug classes beside NRTIs and RAL was lower in the 2 NRTIs group [median IQR: 1 (1–2) compared with the <2 NRTI group: median (IQR): 2 (1–2), P Wilcoxon < 0.001].

As shown in Figure 1, most patients with 2 and <2 NRTIs additionally received a boosted PI, 66.7% and 80.3% ($P = 0.102$). Most patients with a boosted PI received DRV (74.3%). NNRTIs also were often co-administered, in 44.4% (2 NRTIs group) and 68.4% (<2 NRTIs group) of cases ($P = 0.007$). Patients with a NNRTI most often had ETV (88.2%). MAR and T20 were rarely administered (3.7% and 18.4%, $P = 0.014$; 3.7% and 6.6%, $P = 0.699$).

In the 2 NRTIs group, the predominant NRTI combination was 3TC/FTC and TDF (38/54, 70.4%), followed by ABC and 3TC (14.8%), ABC and TDF (11.1%), TDF and DDI, and 3TC and zidovudine (each 1.9%). Patients with 1 NRTI most often received 3TC (16/38, 42.1%) or TDF (15/38, 39.5%). Three patients received ABC (7.9%), 2 DDI (5.3%), and 1 each AZT and stavudine (2.6%).

Estimated Genotypic Activity of the Salvage Therapy

The GSS of all non-NRTI drugs in the salvage therapy was lower in the 2 NRTIs group with a median GSS of 2 (1.5–2.5) compared with 2.5 (2–3) ($P < 0.001$). However, when also considering the GSS of NRTIs, the overall GSS of the

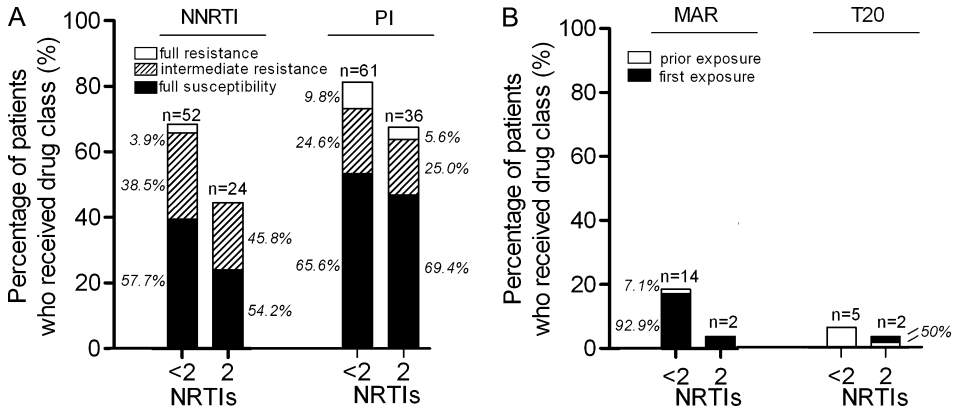

FIGURE 1. Background regimen of patients who receive <2 and 2 NRTI in addition to RAL. A, Percentage of patients who received NNRTI or PI, the proportions of drugs of full resistance, intermediate resistance, or full susceptibility are indicated in italics. B, Percentage of patients who received MAR or T20, the proportions of prior exposure are indicated in italics.

treatment tended to be higher in the 2 NRTIs group 3 (2.5–3.0) compared with 2.5 (2–3, $P = 0.059$).

The contribution to the GSS of each NRTI was similar in the <2 NRTIs and the 2 NRTIs group, the GSS was <0.5, 0.5, and >0.5 in 46.3%, 31.5%, and 22.2% compared with 47.4%, 31.6%, and 21.1% ($P = 1.000$) cases. Most patients (47/63, 74.6%) receiving 3TC/FTC had viral strains carrying the M184I/V mutations, in the <2 and 2 NRTIs group 81.3% and 76.6%, respectively.

Virological Outcome

The described differences in salvage therapy composition and in particular the higher number of drug classes included in the <2 NRTIs group are possibly interfering with our aim to measure the effect of partially active or inactive NRTIs. For this purpose, a marginal structural model was performed. The model creates a "pseudopopulation" in which group differences in salvage treatment composition are balanced.

With the LOCF approach, the crude percentages of patients who achieved viral suppression at week 24 were 72.2% and 71.0% for patients with 2 and <2 NRTIs, respectively. The median (IQR) week of measurement was 24 (20–27) and similar between patients with 2 and <2 NRTIs [24.1 (19.9–26.6) compared with 23.9 (20.1–27.5)]. About 2.6% (2 NRTIs group) and 5.6% (<2 NRTIs group) had no RNA measurement performed. A similar number of patients stopped, interrupted, or changed treatment before week 24, 22.2% (12 of 54) and 29.0% (22 of 76) in the 2 and <2 NRTIs group, respectively ($P = 0.425$). Toxicity was the reason for the change among 16.7% (2 of 12) and 36.4% (8 of 22) of the cases ($P = 0.430$). As shown in Figure 2, multivariable logistic regressions showed that patients treated with <2 NRTIs compared with 2 NRTIs had a decreased chance to achieve viral suppression [multivariable odds ratio (OR): 0.59, $P = 0.269$; weighted multivariable OR: 0.34, $P = 0.027$] (Table 3). The robustness of the results was tested with a bootstrap analysis (1000 replications), it yielded a similar result [mean multivariable weighted OR: 0.41 (fifth and 95th percentiles: 0.11–0.98)], suggesting that the observed differences were not hinging on a few specific observations in our dataset but were broadly consistent.

The crude percentage of patients with suppressed viral load was slightly lower when using the m = f approach (2 NRTIs: 64.8%, <2 NRTIs: 59.2%). The beneficial effect of 2 NRTIs was confirmed in multivariable (OR: 0.47, $P = 0.099$), and in weighted multivariable models (OR: 0.33, $P = 0.027$) (Fig. 2). Also the per-protocol analysis confirmed results. Eighty-three patients were included who did not change, stop, or interrupt treatment until week 24 and who had a viral load measurement performed within the given time frame (multivariable OR: 0.54, $P = 0.337$, weighted multivariable OR: 0.19, $P = 0.023$).

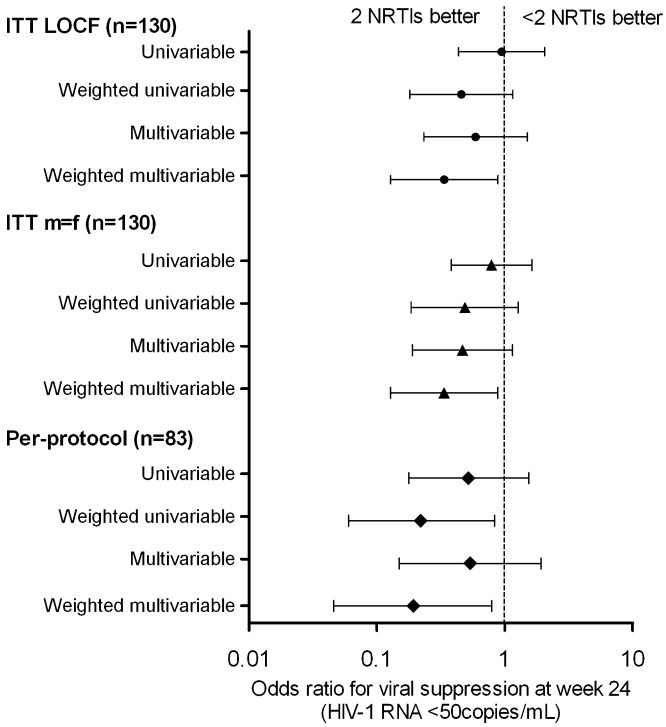

FIGURE 2. Logistic regression was performed to compare the viral suppression rate at week 24 between patients treated with <2 NRTIs or 2 NRTIs in a salvage treatment with RAL. Different approaches were compared: intent-to-treat analysis with missing equal failure (ITT m = f), ITT LOCF and a per-protocol analysis.

TABLE 3. Weighted Multivariable Logistic Regression Analyzing Virological Suppression at Week 24

Characteristics	HIV-1 RNA < 50 Copies/mL (n = 93)	HIV-1 RNA ≥ 50 Copies/mL (n = 37)	Weighted Multivariable OR (95% CI)	*P*
Number of NRTIs				
2	39 (72.2%)	15 (27.8%)	1 (Ref)	—
<2	54 (71.0%)	22 (28.9%)	0.34 (0.13 to 0.89)	0.027
Sex				
Male	66 (70.2%)	28 (29.8%)	1 (Ref)	—
Female	27 (75.0%)	9 (25.0%)	2.19 (0.57 to 8.45)	0.254
Ethnicity				
White	79 (71.8%)	31 (28.2%)	1 (Ref)	—
Other	14 (70.0%)	6 (30.0%)	1.10 (0.30 to 4.01)	0.887
Transmission category				
IDU	14 (70.0%)	6 (30.0%)	1.38 (0.41 to 4.65)	0.608
Other	79 (71.8%)	31 (28.2%)	1 (Ref)	—
Median (IQR) age (in yrs)	48 (41–51)	44 (41–48)	1.10 (1.03 to 1.17)	0.002
Median (IQR) HIV-1 RNA (log_{10} copies/mL)	4.2 (3.3–4.7)	4.7 (3.8–5.1)	0.51 (0.29 to 0.87)	0.015
CD4 count (cells/μL)				
<200	39 (69.6%)	17 (30.4%)	1 (Ref)	—
≥200	54 (73.0%)	20 (27.0%)	0.91 (0.36 to 2.32)	0.850
GSS of the treatment (without NRTIs)				
0–1.5	14 (56.0%)	11 (44.0%)	1 (Ref)	—
2–2.5	54 (77.1%)	16 (22.9%)	3.17 (0.83 to 12.1)	0.092
≥3	25 (71.4%)	10 (28.6%)	4.04 (0.55 to 29.9)	0.172
Median (IQR) drug classes	3 (2–3)	3 (2–3)	1.17 (0.50 to 2.74)	0.711

MSM, men who have sex with men.

Different sensitivity analyses were performed to verify the results. Because the higher GSS of NRTIs in the 2 NRTIs group might partially explain the results, a subanalysis including only patients with a cumulative NRTI GSS ≤0.5 in the regimen was performed (n = 93 ITT LOCF, n = 60 per protocol). It was confirmed that additional NRTIs with low activity are beneficial for virological outcome (ITT LOCF: weighted multivariable OR: 0.13, 95% CI: 0.03 to 0.55; per protocol: OR: 0.06, 95% CI: 0.01 to 0.38). Because the last GRT was not always performed immediately before RAL start, the estimation of the GSS might be imprecise. Therefore, a logistic regressions including exclusively patients who had a GRT on the last failing regimen was performed [ITT LOCF (n = 104): weighted multivariable OR: 0.36, 95% CI: 0.11 to 1.18, per protocol (n = 65): OR: 0.07, 95% CI: 0.01 to 0.46].

As an additional analysis, time to viral suppression was studied. Patients were included if they had at least 1 RNA measurement performed before treatment change, stop, or interruption (n = 109). The frequency of RNA measurements after RAL start was similar between groups (data not shown). Compared with patients with 2 NRTIs, patients with <2 NRTIs had a longer time to viral suppression. The hazard ratio with the multivariable and weighted multivariable regression was 0.63 (95% CI: 0.39 to 1.03, $P = 0.064$) and 0.54 (95% CI: 0.37 to 0.80, $P = 0.002$), respectively.

DISCUSSION

The availability of second-line antiretroviral agents and the introduction of new drug classes increased the options for salvage treatment markedly and raised the question of the optimal combination of compounds. Particularly, the role of genotypic partially or completely inactive NRTIs in such situations is unknown. In our study, we saw that NRTIs were often replaced by other drug classes, such as second-line NNRTIs, boosted PIs, T20, or MAR. Importantly, patients who received 2 inactive or partially active NRTIs were more likely to achieve viral suppression at week 24. These NRTIs might have a residual antiretroviral activity or select viruses with reduced replicative capacity, which might be favorable to achieve viral suppression.[9] The presence of 2 NRTIs increased the chance to achieve viral suppression three times. Single NRTI did not significantly increase the chance to achieve viral suppression but tended to show an additional benefit compared with NRTI-sparing regimen (data not shown). Also the time to viral suppression was faster when 2 NRTIs were given. A short time to suppression might be beneficial because it may decrease the chance to accumulate resistance associated mutations in the very early phase of therapy. These findings were consistent and were confirmed with different approaches and sensitivity analyses.

The use of NRTIs in salvage therapies has several potential advantages. In contrast to new compounds, NRTIs are well studied after 20 years of use: Their long-term toxicities are well characterized, and the potential for drug-drug interactions is low. Costs are much lower compared with newer antiretroviral compounds, which are particularly relevant for developing countries and will become more important in the future when generic antiretroviral agents will be available.

Previous studies showed that NRTI-sparing regimens suppress viremia in treatment-naive and treatment-experienced patients but increase the probability to select for drug resistance mutations. They reduce the frequency of lipoatrophy, but other adverse events occurred when combining remaining drug classes, (eg, PIs and NNRTIs).[32–36]

Preliminary results from another study addressing the effect of inactive NRTIs in salvage therapy are in contradiction with our findings. However, in contrast to our study, no adherence data were available, no weighting was performed, the number of patients with <2 NRTIs was very small (27 compared with 76 in our study) and it was not differentiated between patients receiving salvage treatment with RAL, MAR, or ETV.[37]

We used marginal structural models to overcome confounding by indication. The model performed in this study simulated a hypothetical randomized controlled trial in which patients were randomly assigned to receive a treatment with <2 or 2 NRTIs. As in any observational studies, it is impossible to exclude unmeasured confounding. In particular, we cannot fully exclude that there were additional factors, which led physicians to choose a treatment with <2 NRTIs, but which were also associated with a worse treatment outcome. However, in absence of a randomized controlled trial, observational studies represent the best available evidence. To analyze long-term effects and NRTI-related toxicities, large cohort collaborations will be needed.

The possibility to maintain NRTI in the salvage regimen despite the presence of major drug resistance mutation is of high relevance because the drug pipeline of new antiretroviral agents starts to decline and on a global scale resistance will continue to accumulate.[38–41]

To summarize, our study demonstrated that partially active or inactive NRTIs showed a beneficial effect on the short-term virological outcome in patients receiving RAL. Therefore, our study supports the strategy to administer 2 NRTIs in salvage therapy with RAL even if inactive or only partially active according to GSS. The negative impact on viral fitness by maintaining drug resistance mutations and the residual activity of NRTIs must not be underestimated. However, the benefit of these NRTIs should be balanced with potential complications because complex antiretroviral regimens can be associated with increased toxicity or poor adherence. Further studies and collaborations are needed to support our findings and to analyze the long-term benefit of partially active or inactive NRTIs.

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APPENDIX I: MEMBERS OF THE SHCS

The members of the SHCS are Battegay M, Bernasconi E, Böni J, Bucher HC, Bürgisser P, Calmy A, Cattacin S, Cavassini M, Dubs R, Egger M, Elzi L, Fischer M, Flepp M, Fontana A, Francioli P (President of the SHCS), Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (Chairman of the Scientific Board), Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Karrer U, Kind C, Klimkait T, Ledergerber B, Martinetti G, Müller N, Nadal D, Paccaud F, Pantaleo G, Rauch A, Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Schultze D, Schüpbach J, Speck R, de Tejada BM, Taffé P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.