Journal of Antimicrobial Chemotherapy

*J Antimicrob Chemother* 2015; **70**: 3323–3331
doi:10.1093/jac/dkv257 Advance Access publication 11 September 2015

# Assessing efficacy of different nucleos(t)ide backbones in NNRTI-containing regimens in the Swiss HIV Cohort Study

**Wan-Lin Yang[1,2], Roger D. Kouyos[1,2], Alexandra U. Scherrer[1,2], Jürg Böni[3], Cyril Shah[3], Sabine Yerly[4], Thomas Klimkait[5], Vincent Aubert[6], Cédric Hirzel[7], Manuel Battegay[8], Matthias Cavassini[9], Enos Bernasconi[10], Pietro Vernazza[11], Leonhard Held[12], Bruno Ledergerber[1,2] and Huldrych F. Günthard[1,2]* on behalf of the Swiss HIV Cohort Study (SHCS)†**

*[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [2]Institute of Medical Virology, University of Zurich, Zurich, Switzerland; [3]Swiss National Center for Retroviruses, Institute of Medical Virology, University of Zurich, Zurich, Switzerland; [4]Laboratory of Virology, Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland; [5]Department of Biomedicine-Petersplatz, University of Basel, Basel, Switzerland; [6]Division of Immunology and Allergy, University Hospital Lausanne, Lausanne, Switzerland; [7]Department of Infectious Diseases, Berne University Hospital and University of Berne, Berne, Switzerland; [8]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland; [9]Division of Infectious Diseases, University Hospital Lausanne, Lausanne, Switzerland; [10]Division of Infectious Diseases, Regional Hospital Lugano, Lugano, Switzerland; [11]Division of Infectious Diseases, Cantonal Hospital St Gallen, St Gallen, Switzerland; [12]Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland*

*Corresponding author. Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. Tel: +41-44-255-1111; Fax: +41-44-255-3291; E-mail: huldrych.guenthard@usz.ch
†Members are listed in the Acknowledgements section.

*Received 8 May 2015; returned 23 June 2015; revised 16 July 2015; accepted 26 July 2015*

**Background:** The most recommended NRTI combinations as first-line antiretroviral treatment for HIV-1 infection in resource-rich settings are tenofovir/emtricitabine, abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine. Efficacy studies of these combinations also considering pill numbers, dosing frequencies and ethnicities are rare.

**Methods:** We included patients starting first-line combination ART (cART) with or switching from first-line cART without treatment failure to tenofovir/emtricitabine, abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine plus efavirenz or nevirapine. Cox proportional hazards regression was used to investigate the effect of the different NRTI combinations on two primary outcomes: virological failure (VF) and emergence of NRTI resistance. Additionally, we performed a pill burden analysis and adjusted the model for pill number and dosing frequency.

**Results:** Failure events per treated patient for the four NRTI combinations were as follows: 19/1858 (tenofovir/emtricitabine), 9/387 (abacavir/lamivudine), 11/344 (tenofovir/lamivudine) and 45/1244 (zidovudine/lamivudine). Compared with tenofovir/emtricitabine, abacavir/lamivudine had an adjusted HR for having VF of 2.01 (95% CI 0.86–4.55), tenofovir/lamivudine 2.89 (1.22–6.88) and zidovudine/lamivudine 2.28 (1.01–5.14), whereas for the emergence of NRTI resistance abacavir/lamivudine had an HR of 1.17 (0.11–12.2), tenofovir/lamivudine 11.3 (2.34–55.3) and zidovudine/lamivudine 4.02 (0.78–20.7). Differences among regimens disappeared when models were additionally adjusted for pill burden. However, non-white patients compared with white patients and higher pill number per day were associated with increased risks of VF and emergence of NRTI resistance: HR of non-white ethnicity for VF was 2.85 (1.64–4.96) and for NRTI resistance 3.54 (1.20–10.4); HR of pill burden for VF was 1.41 (1.01–1.96) and for NRTI resistance 1.72 (0.97–3.02).

**Conclusions:** Although VF and emergence of resistance was very low in the population studied, tenofovir/emtricitabine appears to be superior to abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine. However, it is unclear whether these differences are due to the substances as such or to an association of tenofovir/emtricitabine regimens with lower pill burden.

## Introduction

More than 25 antiretroviral drugs from 6 different drug classes against HIV-1 infection are available today. The standard combination ART (cART) consists of two NRTIs and a potent third agent, e.g. an NNRTI.[1] Recent guidelines recommend tenofovir/emtricitabine or abacavir/lamivudine in combination with either efavirenz or nevirapine, or rilpivirine for individuals with

HIV-1-RNA <100 000 copies/mL as the preferred NRTI backbone for first-line cART including NNRTI.[1,2] Alternatively, if unavailability or intolerance exists, tenofovir/lamivudine and zidovudine/lamivudine are recommended.[3,4] These were used in first-line regimens before the availability of tenofovir/emtricitabine and abacavir/lamivudine as fixed-dose combinations and are still widely used in resource-limited settings.

Studies directly comparing all these four NRTI combinations in large populations are lacking and the relative *in vivo* efficacy is unclear. Zidovudine/lamivudine showed similar potency as tenofovir/emtricitabine plus efavirenz in a randomized controlled trial,[5] but is no longer a first-line option due to toxicity[6] and twice-daily dosing.[7] Although abacavir/lamivudine and tenofovir/emtricitabine were found to provide comparable antiretroviral efficacy as first-line treatment in a randomized trial,[8] in another clinical trial abacavir/lamivudine showed inferior virological responses compared with tenofovir/emtricitabine in patients with baseline HIV-RNA levels >100 000 copies/mL[9,10] and abacavir/lamivudine was also associated with more adverse events including lipid abnormalities.[10] Moreover, some randomized trials observed better virological responses for regimens containing tenofovir/emtricitabine than tenofovir/lamivudine,[11] whereas other studies[12,13] observed equal suppression rates. A recent observational study comparing treatment-naive patients initiating tenofovir/lamivudine or tenofovir/emtricitabine plus an NNRTI found that tenofovir/lamivudine led to more virological failures (VFs); however, this study did not consider adherence, pill counts or dosing frequency as potential confounders.[14]

Comparing NRTI backbones is a complex undertaking because they are formulated differentially: for tenofovir/emtricitabine and abacavir/lamivudine once daily and for zidovudine/lamivudine twice daily fixed-dose combinations exist. Efavirenz can be given in combination with tenofovir/emtricitabine, but is mostly used as a single-tablet regimen including efavirenz/tenofovir/emtricitabine. In addition, lamivudine can be taken once or twice daily in contrast to emtricitabine, which has exclusively the once-daily option. Thus, the daily number of total pills and the maximal dosing frequency can vary substantially among zidovudine, abacavir, emtricitabine, lamivudine and tenofovir in NNRTI-containing regimens. Randomized clinical trials mostly compare just two backbones. They do not necessarily reflect a routine clinical setting because patients are often highly selected due to strict enrolment criteria and men are enrolled over-proportionally in general. However, it is important to examine the treatment efficacy of NRTI backbones with regard to pill burden and dosing frequency, since governments, health insurers and third-party payers may soon start to put pressure on using also non-coformulated ART generics in the future due to considerably lower prices.

The aim of this study was to compare tenofovir/emtricitabine, abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine paired with efavirenz or nevirapine as first-line cART regarding virological responses and emergence of NRTI resistance in the representative Swiss HIV Cohort Study (SHCS) and to evaluate the impact of pill burden and dosing frequency on treatment efficacy.

## Methods

### Selection of patients

Our analysis was based on ART-experienced patients from the SHCS starting treatment up to 8 January 2014. The SHCS, continuously enrolling patients aged 16 or older since 1988, is a prospective and nationwide cohort study including a biobank. The SHCS is representative of the HIV epidemic in Switzerland; it includes at least 53% of all HIV cases ever diagnosed in Switzerland, 72% of all patients receiving ART and 69% of the nationwide registered AIDS cases.[15] Local ethics committees have approved the SHCS for all participating institutions and written informed consent was obtained from all patients.[15,16]

Resistance data are generated from routine clinical testing performed by four laboratories authorized by the Swiss Federal Office of Public Health. All laboratories sequenced the full protease gene and at least codons 28–225 of the reverse transcriptase gene using population-based sequencing with commercial assays (Viroseq Vs.1, PE Biosystems; Viroseq Vs. 2, Abbott AG; VircoTYPE HIV-1 Assay, Virco Lab) or in-house methods.[17] They all participate in the annual quality control evaluation by the Agence Nationale de la Recherche sur le SIDA et les hépatites virales (ANRS) since 2002. All sequences are entered into the SHCS drug-resistance database using SmartGene's Integrated Database Network System (SmartGene, Zug, Switzerland, IDNS version 3.6.3).[18] Additionally, we systematically selected and retrospectively sequenced plasma samples from treatment-naive and treatment-failing patients stored in our biobank, especially for samples obtained before routine genotyping was introduced in 2002.

To compare the efficacy of the different NRTI backbones (tenofovir/emtricitabine, abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine) combined with either efavirenz or nevirapine, we identified HIV-1-infected patients from the SHCS who had initiated their first cART with one of the regimens mentioned above or switched from their first cART to one of these regimens for reasons other than treatment failure. Patients were excluded from the analysis if baseline resistance was identified according to the Stanford database algorithm (mutation penalty score ≥15, Stanford genotypic resistance interpretation algorithm version 7.0: http://sierra2.stanford.edu/sierra/servlet/JSierra).

Furthermore, we assessed tablet usage for pill burden analysis, i.e. whether the three drugs in a regimen were prescribed separately or combined. Patients without complete documentation of this usage information were excluded from pill burden analysis.

### Study outcomes

Two primary outcomes were analysed: VF and emergence of NRTI resistance, which was defined as the first detection of any major IAS-USA drug resistance mutation[19] to NRTI following VF. VF was defined as HIV-1 plasma RNA level ≥400 copies/mL after 180 days of continuous treatment. If the subsequent HIV-RNA was <400 copies/mL, it was considered a viral blip and not a VF. Not all patients experiencing VF had a genotypic resistance test (GRT) performed following VF. Including subjects in the resistance analysis for whom we could not determine whether or not resistance had emerged would potentially be incorrect because they would be included as if they did not have any resistance. Thus, we first compared the characteristics of those with and without GRT following VF within the same regimen group by the Wilcoxon rank-sum test. Variables tested were treatment length, time from treatment initiation to VF, viral load at VF and the consecutive viral load at VF. If there was no evidence for a difference we excluded those with VF, but without GRT, from the resistance analysis.

### Statistical methods

We analysed data with univariable and multivariable Cox proportional hazards models to estimate HRs with 95% CIs and used robust standard errors to account for possible intra-patient correlations because a patient could be included twice: (i) first-line cART; and (ii) switched from first-line cART while suppressed. Exposure time started at treatment initiation for every treatment episode. Patients were censored at the time of death, the last visit date or the end of the treatment, whichever came first. Regimens were included categorically in the model.

Adjustment comprised all variables with univariable significance, which included age (continuous), ethnicity (white/non-white) and treatment initiation year (continuous), and variables decided *a priori*, including baseline HIV-RNA ($log_{10}$ transformed, continuous) and baseline CD4 counts (square-root transformed, continuous). Baseline CD4 and HIV-RNA data at the initiation of the first cART were retrieved. Missing baseline CD4 (5%) and HIV-RNA (7%) were imputed using multivariable normal regression (an iterative Markov chain Monte Carlo method) and estimated by age, sex, ethnicity, inclusion centre, transmission route and treatment initiation year. In the pill burden analysis, models were adjusted for two more co-variables: pill burden (i.e. the total pill number per day, continuous) and the maximal dosing frequency per day (once/twice daily); both were time-updated variables. Since CD4 counts or pill burden entered categorically did not improve the model fit, we treated them as continuous. Collinearity was tested with variance inflation factors and correlation matrices and none was found.

We performed two sensitivity analyses in which we either restricted NNRTI drugs to efavirenz or our study population to patients on first-line cART.

The analyses were performed using Stata 13.0 SE (StataCorp, TX, USA).

## Results

### *Study population*

Since 1996, 9755 patients have been ART-experienced in the SHCS. Among these individuals, 2678 had initiated treatment containing one of the regimens of interest and 1338 had switched from any regimen to one of the regimens of interest. Ninety-nine (7%) patients from the switching group were excluded due to VF or drug resistance identified at switching. This resulted in 3917 treatment episodes from 3398 individuals. Baseline GRT was available for 2477/3398 (73%) patients. Resistance to the prescribed regimen occurred in 77/3398 (2%) patients and these were excluded. In total, our study comprised 3833 treatment episodes from 3321 individuals (Figure 1). Baseline characteristics are summarized in Table 1. Overall, differences among groups were observed in all characteristics except for ethnicity.

### *VFs*

The following numbers of VFs were observed for the different NRTI backbones (Figure 2a and Table 1): tenofovir/emtricitabine, 19 failures from 1858 treatment episodes (1.0%); abacavir/lamivudine, 9 from 387 (2.3%); tenofovir/lamivudine, 11 from 344 (3.2%); zidovudine/lamivudine, 45 from 1244 (3.6%).

In the univariable model the lowest failure rate was observed for tenofovir/emtricitabine (as reference), followed by abacavir/lamivudine [HR 2.38 (95% CI 1.07–5.26), $P=0.033$], tenofovir/lamivudine [HR 4.04 (1.92–8.48), $P<0.001$], zidovudine/lamivudine [HR 3.89 (2.26–6.69), $P<0.001$] (Table 2, left part). After adjustment for baseline CD4, baseline HIV-1 RNA and all significantly associated co-variables, including age, ethnicity and treatment initiation year, HRs among regimens decreased in magnitude [abacavir/lamivudine, 2.01 (0.86–4.55), $P=0.095$; tenofovir/lamivudine, 2.89 (1.22–6.88), $P=0.016$; zidovudine/lamivudine, 2.28 (1.01–5.14), $P=0.046$]. Ethnicity was strongly associated with treatment outcome: non-white patients were 2.67 times more likely to experience VF than white patients (95% CI 1.69–4.23, $P<0.001$).

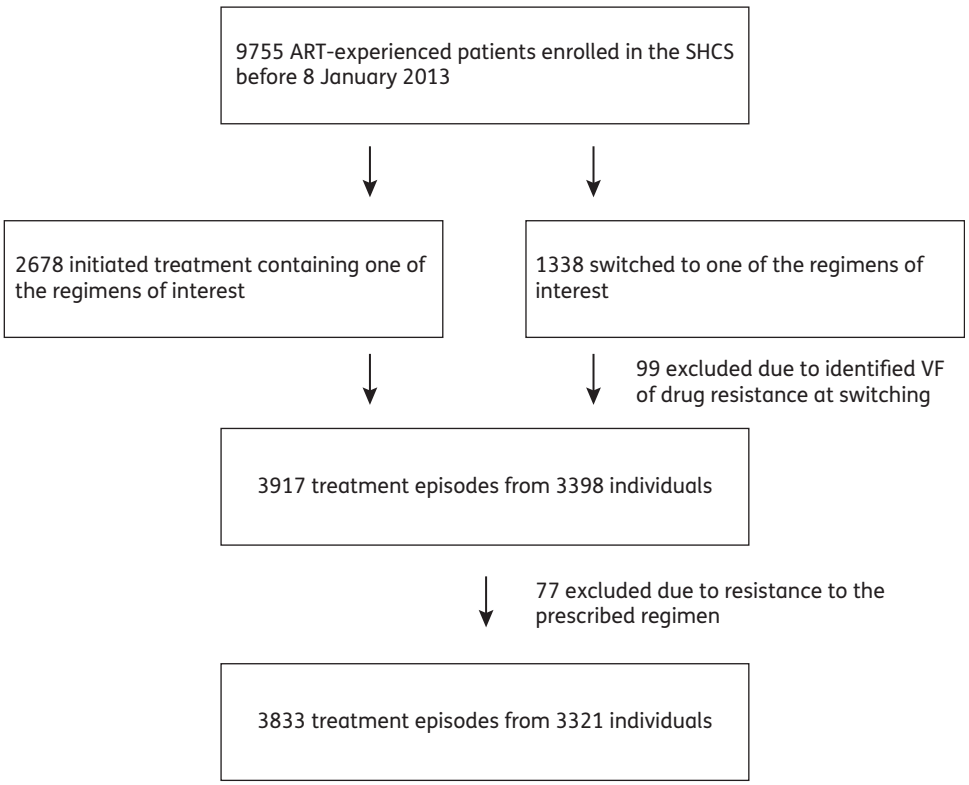


**Figure 1.** Patient selection.

**Table 1.** Baseline characteristics of study population

| | Treatment group | | | | |
|---|---|---|---|---|---|
| | TDF/FTC | ABC/3TC | TDF/3TC | ZDV/3TC | $P^a$ |
| Patients ($N=3321$), *n* (%) | 1577 (47.5) | 274 (8.3) | 268 (8.1) | 1202 (36.2) | |
| Age at baseline (years), median (IQR) | 40 (32–46) | 40 (33–48) | 39 (32–45) | 37 (31–44) | 0.001 |
| Ethnicity, *n* (%) | | | | | 0.142 |
| white | 1171 (74.2) | 190 (69.3) | 204 (76.1) | 862 (71.7) | |
| non-white | 406 (25.8) | 84 (30.7) | 64 (23.9) | 340 (28.3) | |
| Gender and transmission route, *n* (%) | | | | | 0.001 |
| MSM | 873 (55.4) | 114 (41.6) | 94 (35.1) | 387 (32.2) | |
| heterosexual men | 314 (19.9) | 67 (24.5) | 63 (23.5) | 285 (23.7) | |
| heterosexual women | 252 (16.0) | 60 (21.9) | 73 (27.2) | 310 (25.8) | |
| IVDU | 69 (4.4) | 18 (6.6) | 29 (10.8) | 157 (13.1) | |
| unknown | 69 (4.4) | 15 (5.5) | 9 (3.4) | 63 (5.2) | |
| CD4 count at baseline (cells/mm$^3$), median (IQR) | 282 (190–383) | 250 (173–343) | 200 (104–287) | 208 (122–313) | 0.001 |
| Viral load at baseline ($\log_{10}$ copies/mL), median (IQR) | 4.5 (3.5–5.0) | 4.2 (2.6–4.9) | 4.7 (3.6–5.3) | 4.7 (3.9–5.3) | 0.001 |
| Treatment episodes ($N=3833$), *n* (%) | 1858 (48.5) | 387 (10.1) | 344 (9.0) | 1244 (32.5) | |
| Treatment initiation year, median (IQR) | 2009 (2008–11) | 2008 (2007–10) | 2005 (2004–06) | 2002 (2000–04) | 0.001 |
| First-line treatments[b], *n* (%) | 1292 (69.5) | 198 (51.3) | 211 (61.3) | 912 (73.4) | <0.001 |
| VFs[c], *n* (%) | 19 (1.0) | 9 (2.3) | 11 (3.2) | 45 (3.6) | |
| Failures without GRT, *n* | 9 | 4 | 1 | 16 | |
| Resistance emergence[c], *n* (%) | 3 (0.2) | 1 (0.3) | 9 (2.6) | 17 (1.4) | |

TDF, tenofovir; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; ZDV, zidovudine; IVDU, intravenous drug use.
[a]Comparisons were made using the $\chi^2$ test or the Kruskal–Wallis rank test.
[b]Percentage in parentheses indicates the ratio to the total number for that specific regimen.
[c]Percentage in parentheses refers to treatment episodes for the corresponding NRTI regimen.

### *Emergence of NRTI resistance*

Next we analysed the relative efficacy of the four NRTI combinations regarding time to the emergence of any NRTI resistance mutation following VF. However, 9 out of 19 (47%) failing regimens with tenofovir/emtricitabine were not genotyped and the numbers of non-genotyped treatments from failing treatments containing abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine, respectively, were 4 out of 9 (44%), 1 out of 11 (9%) and 16 out of 45 (36%). The Wilcoxon rank-sum test did not find an indication of a difference between patients with and without GRT following VF. Because we had no alternative means to determine whether drug resistance had developed in a non-genotyped failure episode, we excluded those without GRT. After exclusion, we detected NRTI resistance in 3 of 1849 (0.2%) tenofovir/emtricitabine-, 1 of 383 (0.3%) abacavir/lamivudine-, 9 of 343 (2.6%) tenofovir/lamivudine- and 17 of 1228 (1.4%) zidovudine/lamivudine-containing treatment episodes (Figure 2b and Table 1).

In the univariable model the HR of abacavir/lamivudine showed no evidence for an effect on the emergence of resistance when compared with tenofovir/emtricitabine [1.72 (0.18–16.5), $P=0.64$], but NRTI resistance was more associated with tenofovir/lamivudine [20.4 (5.49–75.6), $P<0.001$] and zidovudine/lamivudine [9.8 (2.88–33.3), $P<0.001$] (Table 3, left part). The adjusted HR on emergence of NRTI resistance for patients on tenofovir/lamivudine compared with tenofovir/emtricitabine was 11.3 (2.34–55.3, $P=0.003$), but HR was not significantly different for abacavir/lamivudine [1.17 (0.11–12.2), $P=0.90$] or zidovudine/lamivudine [4.02 (0.78–20.7), $P=0.096$]. Ethnicity was strongly associated with the emergence of NRTI resistance [non-white versus white, HR 4.43 (1.85–10.6), $P=0.001$] in both univariable and multivariable analyses.

### *Study population in the pill burden analysis*

Since pill number and dosing frequency were essential for the pill burden analysis, patients without full documentation of tablet usage were excluded, resulting in 3089 treatment episodes from 2685 individuals. Given that pill burden and dosing frequency are time-updated variables, we had 4263 observations in total. Median, minimal and maximal numbers of total pills of cART were 2, 1 and 6, respectively. For the tenofovir/emtricitabine, abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine regimen groups, the median (IQR) number of total pills was 2 (1–2), 2 (2–3), 4 (4–4) and 3 (3–3), respectively, and the

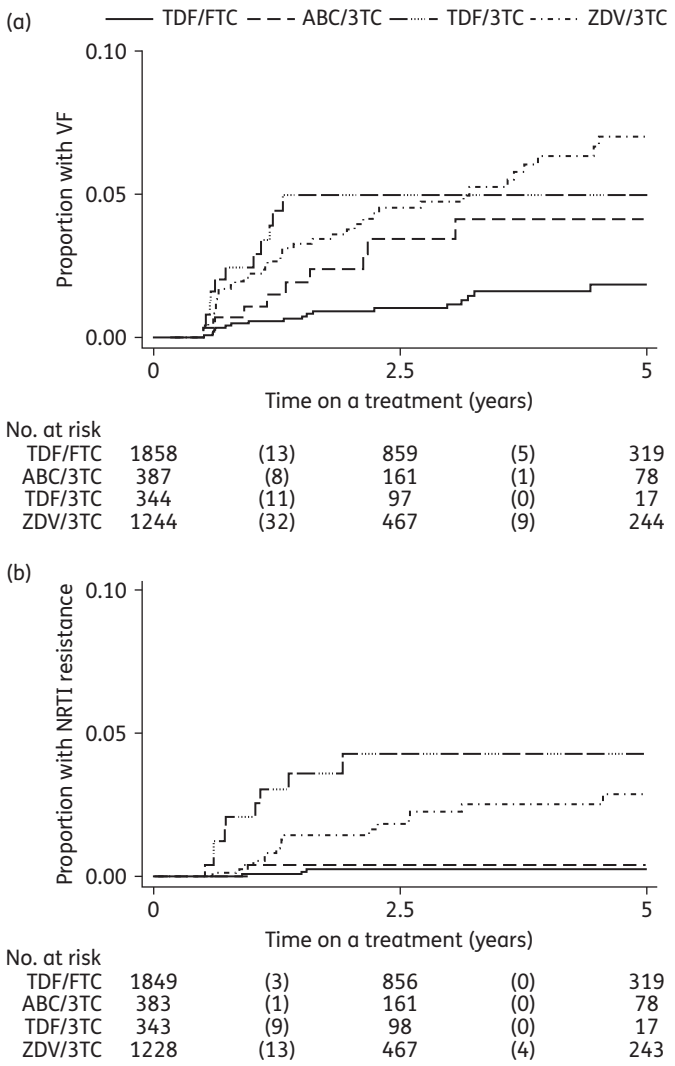


**Figure 2.** Kaplan–Meier curves for time to (a) VF and (b) emergence of NRTI resistance in the different treatment groups. The numbers of failure events are shown in parentheses. TDF, tenofovir; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; ZDV, zidovudine.

proportions of once-daily regimens were 97.2%, 92.5%, 81.0% and 1.4%.

### *VFs in the pill burden analysis*

Similar to the original analysis, the univariable analysis of pill burden resulted in the lowest risk of having VF in the tenofovir/emtricitabine group when compared with the other three regimens [abacavir/lamivudine, HR 2.15 (0.94–4.91), $P=0.069$; tenofovir/lamivudine, 4.29 (2.04–9.05), $P<0.001$; zidovudine/lamivudine, 2.89 (1.48–5.63), $P=0.002$; Table 2, right part]. However, contrary to the original analysis, in which pill burden and dosing frequency were not adjusted for, the multivariable model did not show evidence for differences among regimens [abacavir/lamivudine, HR 1.79 (0.76–4.23), $P=0.18$; tenofovir/lamivudine, 2.64 (0.94–7.44), $P=0.066$; zidovudine/lamivudine, 3.10 (0.51–18.7), $P=0.22$]. Pill burden was associated with VF in both the univariable model [HR 1.69 (1.31–2.19), $P<0.001$; Figure 3a] and the multivariable model [HR 1.41 (1.01–1.96), $P=0.043$]. In addition, non-white ethnicity [HR 2.85 (1.64–4.96), $P<0.001$] remained a strong predictor of having VF after adjustment. In contrast to pill burden, we did not find an association of dosing frequency with VF after adjustment [HR 0.64 (0.12–3.30), $P=0.59$].

### *Emergence of NRTI resistance in the pill burden analysis*

Results followed the same pattern as results on VF in the pill burden analysis. Evidence for effects of tenofovir/lamivudine and zidovudine/lamivudine in the univariable model [abacavir/lamivudine, HR 1.74 (0.18–16.7), $P=0.63$; tenofovir/lamivudine, 21.0 (5.63–78.0), $P<0.001$; zidovudine/lamivudine, 5.84 (1.42–24.1), $P=0.015$; Table 3, right part] was not found after adjustment [abacavir/lamivudine, HR 1.16 (0.10–12.9), $P=0.91$; tenofovir/lamivudine, 5.60 (0.71–44.0), $P=0.10$; zidovudine/lamivudine, 1.62 (0.19–14.1), $P=0.66$; Table 3, right part], but non-white ethnicity remained a strong risk factor [HR 3.54 (1.20–10.4), $P=0.022$]. At the same time, we observed a significant effect of pill burden in the univariable model [HR 2.83 (1.95–4.10), $P<0.001$; Figure 3b] and a trend in the multivariable model [HR 1.72 (0.97–3.02), $P=0.062$]. Dosing frequency, however, showed no effect on the emergence of NRTI resistance [HR 1.19 (0.24–5.82), $P=0.83$].

### *Sensitivity analyses*

Sensitivity analyses, in which we restricted NNRTI to efavirenz or our study population to patients on first-line treatment only, robustly showed qualitatively similar results. After adjusting additionally for pill burden and dosing frequency, evidence for effects of regimens both on VF and on the emergence of NRTI resistance was not detected. However, one distinct exception was observed: the abacavir/lamivudine treatment became a stronger predictor of VF in the model restricted to first-line patients [HR, 2.93 (1.06–8.13), $P=0.039$; pill burden analysis, HR 3.13 (1.10–8.87), $P=0.032$]. Pill burden was consistently observed to have an impact [restricted to first-line patients on VF, HR 1.46 (1.01–2.13), $P=0.046$; on resistance, HR 2.25 (1.21–4.18), $P=0.011$; restricted to efavirenz on VF, HR 1.66 (1.17–2.37), $P=0.005$; on resistance, HR 2.14 (1.04–4.41), $P=0.038$] and non-white ethnicity remained strongly predictive of experiencing VF and emergence of NRTI resistance when restricted to first-line patients [on VF, HR 2.66 (1.56–4.51), $P<0.001$; on resistance, HR 3.32 (1.36–8.15), $P=0.009$; in pill burden analysis on VF, HR 2.71 (1.41–5.21), $P=0.003$; on resistance, HR 2.50 (0.76–8.28), $P=0.13$] and restricted to efavirenz [on VF, HR 2.74 (1.67–4.47), $P<0.001$; on resistance, HR 5.52 (2.01–15.2), $P=0.001$; in pill burden analysis on VF, HR 3.17 (1.72–5.85), $P<0.001$; on resistance, HR 4.89 (1.25–19.2), $P=0.023$].

## Discussion

In this study, we compared VF rates and emergence of NRTI resistance for the four major NRTI combinations tenofovir/emtricitabine, abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine combined with either efavirenz or nevirapine in a real-world clinical setting. Treatment failure rates and frequency of resistance emergence was remarkably low: failure frequencies

**Table 2.** Uni- and multivariable Cox proportional hazards analysis for VF[a]

| | VF | | | | | | VF in pill burden analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | univariable | | | multivariable | | | univariable | | | multivariable | | |
| | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Regimen | | | | | | | | | | | | |
| TDF/FTC | 1 | | | 1 | | | 1 | | | 1 | | |
| ABC/3TC | 2.38 | 1.07–5.26 | 0.033 | 2.01 | 0.86–4.55 | 0.095 | 2.15 | 0.94–4.91 | 0.069 | 1.79 | 0.76–4.23 | 0.18 |
| TDF/3TC | 4.04 | 1.92–8.48 | <0.001 | 2.89 | 1.22–6.88 | 0.016 | 4.29 | 2.04–9.05 | <0.001 | 2.64 | 0.94–7.44 | 0.066 |
| ZDV/3TC | 3.89 | 2.26–6.69 | <0.001 | 2.28 | 1.01–5.14 | 0.046 | 2.89 | 1.48–5.63 | 0.002 | 3.10 | 0.51–18.7 | 0.22 |
| Age, increase per year | 0.97 | 0.95–0.99 | 0.005 | 0.99 | 0.96–1.01 | 0.23 | 0.98 | 0.96–1.01 | 0.22 | 1.00 | 0.97–1.03 | 0.95 |
| Ethnicity | | | | | | | | | | | | |
| white | 1 | | | 1 | | | 1 | | | 1 | | |
| non-white | 2.94 | 1.91–4.53 | <0.001 | 2.67 | 1.69–4.23 | <0.001 | 2.90 | 1.70–4.97 | <0.001 | 2.85 | 1.64–4.96 | <0.001 |
| Gender and transmission route | | | | | | | | | | | | |
| MSM | 1 | | | — | | | 1 | | | — | | |
| heterosexual men | 2.23 | 1.28–3.88 | 0.005 | — | | | 2.21 | 1.16–4.19 | 0.015 | — | | |
| heterosexual women | 1.84 | 1.00–3.38 | 0.051 | — | | | 1.61 | 0.76–3.40 | 0.22 | — | | |
| IVDU | 2.24 | 1.04–4.83 | 0.040 | — | | | 1.24 | 0.37–4.21 | 0.73 | — | | |
| unknown | 2.72 | 1.11–6.68 | 0.029 | — | | | 2.06 | 0.61–7.02 | 0.25 | — | | |
| Square root of CD4 count (cells/μL) | 0.95 | 0.91–0.99 | 0.023 | 0.97 | 0.92–1.02 | 0.30 | 0.95 | 0.90–0.99 | 0.03 | 0.97 | 0.92–1.03 | 0.35 |
| $Log_{10}$ viral load (copies/mL) | 1.14 | 0.95–1.36 | 0.17 | 1.07 | 0.88–1.30 | 0.50 | 1.18 | 0.95–1.46 | 0.13 | 1.13 | 0.89–1.44 | 0.31 |
| Treatment initiation year, increase per year | 0.87 | 0.82–0.92 | <0.001 | 0.94 | 0.85–1.04 | 0.22 | 0.90 | 0.83–0.97 | 0.005 | 1.05 | 0.93–1.19 | 0.40 |
| Pill number per day | — | | | — | | | 1.69 | 1.31–2.19 | <0.001 | 1.41 | 1.01–1.96 | 0.043 |
| Dosing frequency per day | — | | | — | | | 1.81 | 1.02–3.19 | 0.041 | 0.64 | 0.12–3.30 | 0.59 |

TDF, tenofovir; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; ZDV, zidovudine; IVDU, intravenous drug use.
[a]The multivariable models were adjusted for all variables indicated, i.e. showing HR.

ranged from 1.0% for the tenofovir/emtricitabine to 3.6% for the zidovudine/lamivudine treatment group and the rate of NRTI resistance was even lower, ranging from 0.2% for tenofovir/emtricitabine to 2.6% for tenofovir/lamivudine. In univariable and multivariable analyses we found that abacavir/lamivudine-, tenofovir/lamivudine- and zidovudine/lamivudine-containing regimens had a >2-fold higher risk of leading to VF than tenofovir/emtricitabine-containing regimens. Tenofovir/lamivudine was more often associated with emergence of NRTI resistance than tenofovir/emtricitabine. Not taking the pill burden into account, this may suggest superiority of emtricitabine over lamivudine. Among regimens other than tenofovir/emtricitabine, no clear superiority was found. When adjusting for pill burden and dosing frequency, we found that a higher number of pills, but not dosing frequency, was associated with VF and emergence of NRTI resistance. Additionally, a very strong predictor of VF and resistance emergence was non-white ethnicity.

Our results are consistent with a recent meta-analysis showing that lower pill burden was associated with viral suppression.[20] Similarly, patients receiving Atripla (efavirenz/tenofovir/emtricitabine as a single-tablet regimen) had a lower risk of selection for drug resistance compared with patients receiving the same drug components as separate tablets.[21] On the other hand, a large and long-term randomized trial found that twice-daily regimens containing raltegravir performed at least as well as once-daily regimens,[22] demonstrating that, in addition to the convenience of taking a drug regimen, the tolerability of the regimen is also of great importance. In a previous study from the SHCS a higher risk of VF on cART[23] due to inferior self-reported adherence[23,24] in sub-Saharan African patients was observed. Since white patients infected with non-B subtypes showed improved virological outcomes in the SHCS,[25] differences in adherence, but not between subtypes, could possibly explain the strong effect of ethnicity found in our analyses.

Our study included not only treatment-naive patients initiating their first cART, but also patients switching from their first cART. Several potential problems should be noted in this respect. The first of these is that second-line patients started treatment with fully suppressed HIV-1-RNA. As a result, the risk of developing drug resistance could be smaller than for first-line patients because failure during the time to achieve viral suppression was not possible by definition. However, this was the case for all four regimens and a potential bias is unlikely. Second, for patients

**Table 3.** Uni- and multivariable Cox proportional hazards analysis for emergence of NRTI resistance[a]

| | NRTI resistance | | | | | | NRTI resistance in pill burden analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | univariable | | | multivariable | | | univariable | | | multivariable | | |
| | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Regimen | | | | | | | | | | | | |
| TDF/FTC | 1 | | | 1 | | | 1 | | | 1 | | |
| ABC/3TC | 1.72 | 0.18–16.5 | 0.64 | 1.17 | 0.11–12.2 | 0.90 | 1.74 | 0.18–16.7 | 0.63 | 1.16 | 0.10–12.9 | 0.91 |
| TDF/3TC | 20.4 | 5.49–75.6 | <0.001 | 11.3 | 2.34–55.3 | 0.003 | 21.0 | 5.63–78.0 | <0.001 | 5.60 | 0.71–44.0 | 0.10 |
| ZDV/3TC | 9.80 | 2.88–33.3 | <0.001 | 4.02 | 0.78–20.7 | 0.096 | 5.84 | 1.42–24.1 | 0.015 | 1.62 | 0.19–14.1 | 0.66 |
| Age, increase per year | 0.94 | 0.91–0.98 | 0.002 | 0.97 | 0.94–1.01 | 0.21 | 0.96 | 0.92–1.00 | 0.058 | 0.98 | 0.94–1.03 | 0.45 |
| Ethnicity | | | | | | | | | | | | |
| white | 1 | | | 1 | | | 1 | | | 1 | | |
| non-white | 5.41 | 2.55–11.5 | <0.001 | 4.43 | 1.85–10.6 | 0.001 | 3.84 | 1.51–9.78 | 0.005 | 3.54 | 1.20–10.4 | 0.022 |
| Gender and transmission route | | | | | | | | | | | | |
| MSM | 1 | | | — | | | 1 | | | — | | |
| heterosexual men | 2.85 | 1.15–7.10 | 0.024 | — | | | 2.98 | 0.95–9.36 | 0.061 | — | | |
| heterosexual women | 2.48 | 0.93–6.58 | 0.068 | — | | | 2.64 | 0.76–9.11 | 0.13 | — | | |
| IVDU | 0.76 | 0.09–6.11 | 0.80 | — | | | — | — | — | — | | |
| unknown | 2.76 | 0.58–13.0 | 0.20 | — | | | 2.43 | 0.28–21.0 | 0.42 | — | | |
| Square root of CD4 count (cells/μL) | 0.88 | 0.83–0.94 | <0.001 | 0.88 | 0.81–0.96 | 0.002 | 0.88 | 0.81–0.94 | <0.001 | 0.89 | 0.80–1.00 | 0.042 |
| $Log_{10}$ viral load (copies/mL) | 1.03 | 0.73–1.45 | 0.86 | 0.87 | 0.67–1.15 | 0.33 | 1.30 | 0.78–2.19 | 0.32 | 1.05 | 0.60–1.83 | 0.86 |
| Treatment initiation year, increase per year | 0.81 | 0.75–0.87 | <0.001 | 0.91 | 0.78–1.06 | 0.23 | 0.79 | 0.73–0.86 | <0.001 | 0.98 | 0.78–1.24 | 0.90 |
| Pill number per day | — | | | — | | | 2.83 | 1.95–4.10 | <0.001 | 1.72 | 0.97–3.02 | 0.062 |
| Dosing frequency per day | — | | | — | | | 2.33 | 0.91–5.99 | 0.078 | 1.19 | 0.24–5.82 | 0.83 |

TDF, tenofovir; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; ZDV, zidovudine; IVDU, intravenous drug use.
[a]The multivariable models were adjusted for all variables indicated, i.e. showing HR.

whose NRTI backbone was identical in the first and the second cART (i.e. only the third agent was changed), it was possible that drug resistance had developed as minor variants during the first cART, but was not detected. Thus, second-line treatment might have failed sooner than first-line treatment. However, sensitivity analyses including only first-line patients confirmed that our results were robust, apart from the higher HR of abacavir/lamivudine-containing regimens on VF. The higher failure rate for abacavir/lamivudine-containing first-line treatments could again point to a higher activity of emtricitabine compared with lamivudine, but to definitely tease out the superiority of emtricitabine, studies with a larger sample size are needed in determining the relative efficacies of these NRTI combinations.

The strength of this study was its representativeness, due to the following facts: (i) patients' HIV-1 viral loads are monitored regularly at 3 month intervals; (ii) viral loads ≥500 copies/mL are genotyped as routine clinical practice; and (iii) retrospective sequencing was performed on available samples for every failed treatment episode even for patients, who were not genotyped, from earlier times. On the other hand, limitations of our study were that failure events were not numerous enough to differentiate between NRTI backbones more precisely. The pill burden analysis showed that HRs of abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine compared with tenofovir/emtricitabine for having VF and NRTI resistance were indeed all above 1 but had very wide CIs. On this point, it was difficult to determine whether power issues limited our ability to document evidence of regimen effect from the pill burden analysis. Studies with more individuals are needed to evaluate the relative efficacies of the regimens and to disentangle the effects of pill burden and type of regimen. However, even with our sample size we could observe effects of pill burden and ethnicity. Hence, our data suggested that both ethnicity and pill burden were at least equally important as the substances themselves in affecting treatment efficacy and had a decisive impact on VF and the emergence of NRTI resistance.

In conclusion, although VF and the emergence of resistance were very low in the population studied, tenofovir/emtricitabine appeared to be superior to abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine. However, if pill burden and

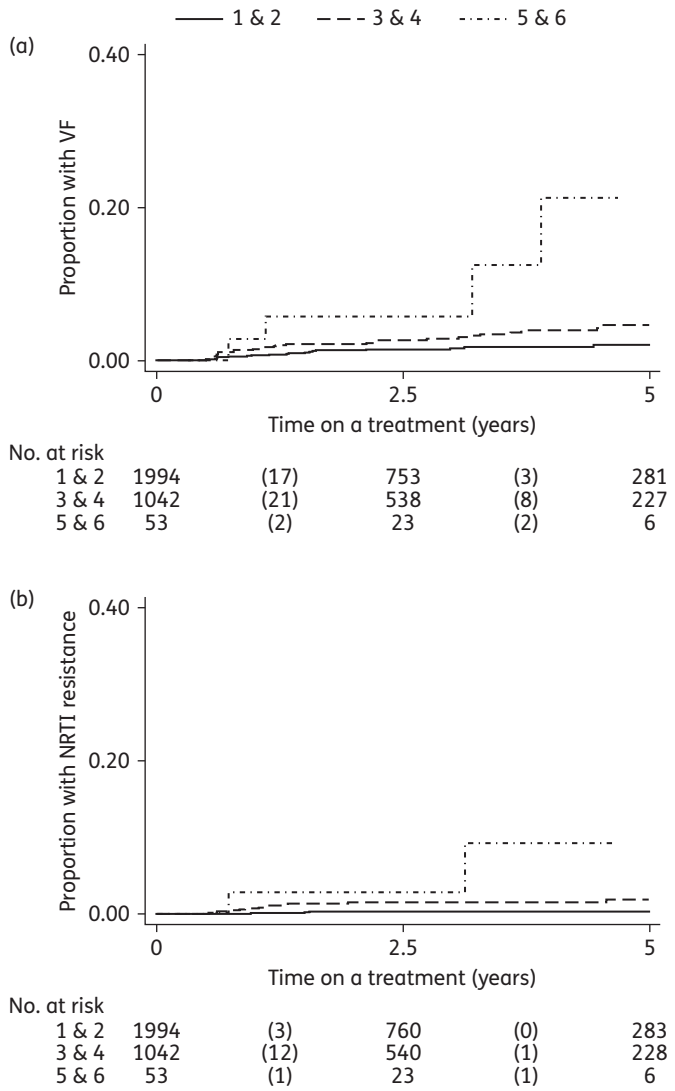


**Figure 3.** Kaplan–Meier curves for time to (a) VF and (b) emergence of NRTI resistance in groups with different pill burdens. For the purpose of clear visualization, pill burden was categorized according to the number of pills per day into three groups: 1–2, 3–4 and 5–6. The numbers of failure events are shown in parentheses.

ethnicity were included in the model these differences became statistically non-significant, illustrating the multifactorial nature of treatment response. Thus, our results indicate a superiority of tenofovir/emtricitabine-containing regimens, but do not allow definitive determination of whether this effect is caused by the lower pill burden or the substances themselves. Finally, our findings are relevant in the light of the upcoming availability of generic drugs. Even when generics are available, the aim of minimizing the pill burden should be maintained.

## Acknowledgements

We thank the patients who participate in the SHCS; the physicians and study nurses for excellent patient care; the resistance laboratories for high-quality genotypic drug-resistance testing; SmartGene, Zug, Switzerland, for technical support; Brigitte Remy, RN, Martin Rickenbach, MD, Franziska Schöni-Affolter, MD and Yannick Vallet, MSc from the SHCS Data Center in Lausanne for data management; and Danièle Perraudin and Mirjam Minichiello for administrative assistance.

### *Members of the Swiss HIV Cohort Study (SHCS)*

Aubert V, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (Deputy of the 'Positive Council'), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rickenbach M (Head of the Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F, Schmid P, Schüpbach J, Speck R, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R and Yerly S.

## Funding

This study has been financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (SNF grant #33CS30-134277) and the SHCS projects #470, 528, 569 and 683, the SHCS Research Foundation, the Swiss National Science Foundation (grant # -159868, to H. F. G.), the European Community's Seventh Framework Program (grant FP7/ 2007–2013), under the Collaborative HIV and Anti-HIV Drug-Resistance Network (CHAIN; grant 223131, to H. F. G.), by the Yvonne-Jacob Foundation, by a further research grant of the Union Bank of Switzerland, in the name of an anonymous donor to H. F. G., an unrestricted research grant from Gilead, Switzerland to the SHCS Research Foundation and by the University of Zurich's Clinical Research Priority Program (CRPP) 'Viral Infectious Diseases: Zurich Primary HIV Infection Study' (to H. F. G.). R. D. K. was supported by SNF # PZ00P3-142411. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

## Transparency declarations

S. Y. has been a consultant for Bristol-Myers Squibb and has received unrestricted research and educational grants from Roche, ViiV and Gilead. T. K. has served as an advisor for Bristol-Myers Squibb and Pfizer, and has received travel grants from Abbott and Pfizer. C. H. has received a travel grant from Janssen-Cilag. E. B. has been a consultant for Bristol-Myers Squibb, Gilead, ViiV Healthcare, Pfizer, MSD and Janssen, has received unrestricted research grants from Gilead, Abbott, Roche and MSD, and has received travel grants from Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, MSD and Janssen. L. H. has been a consultant for Roche and Nycomed (now owned by Takeda Pharmaceutica). B. L. has received travel grants, grants or honoraria from Bristol-Myers Squibb, Gilead, Pfizer, ViiV, Merck Sharp & Dohme and Janssen. H. F. G. has been an adviser and/or consultant for the following companies: GlaxoSmithKline, Abbott, Gilead, Novartis, Boehringer Ingelheim, Roche, Tibotec, Pfizer and Bristol-Myers Squibb, and has received unrestricted research and educational grants from Roche, Abbott, Bristol-Myers Squibb, Gilead, AstraZeneca, GlaxoSmithKline and Merck Sharp & Dohme (all money went to institution). All other authors: none to declare.

## References

**1** Günthard HF, Aberg JA, Eron JJ *et al*. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. *JAMA* 2014; **312**: 410–25.

**2** Thompson MA, Aberg JA, Hoy JF *et al*. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA Panel. *JAMA* 2012; **308**: 387–402.

**3** WHO. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. 2013. http://www.who.int/hiv/pub/guidelines/arv2013/en/.

**4** European AIDS Clinical Society. *EACS Guidelines*. 2014. http://www.eacsociety.org/files/guidelines-7.1-english.pdf.

**5** Campbell TB, Smeaton LM, Kumarasamy N *et al*. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. *PLoS Med* 2012; **9**: e1001290.

**6** Richman DD, Fischl MA, Grieco MH *et al*. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med* 1987; **317**: 192–7.

**7** Hammer SM, Eron JJ, Reiss P *et al*. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society–USA Panel. *JAMA* 2008; **300**: 555–70.

**8** Smith KY, Patel P, Fine D *et al*. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS Res Hum Retroviruses* 2009; **23**: 1547–56.

**9** Thompson MA, Aberg JA, Cahn P *et al*. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA Panel. *JAMA* 2010; **304**: 321–33.

**10** Sax PE, Tierney C, Collier AC *et al*. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med* 2009; **361**: 2230–40.

**11** Tang MW, Kanki PJ, Shafer RW. A review of the virological efficacy of the 4 World Health Organization-recommended tenofovir-containing regimens for initial HIV therapy. *Clin Infect Dis* 2012; **54**: 862–75.

**12** Ford N, Shubber Z, Hill A *et al*. Comparative efficacy of lamivudine and emtricitabine: a systematic review and meta-analysis of randomized trials. *PLoS One* 2013; **8**: e79981.

**13** Wang Q, Young J, Bernasconi E *et al*. Virologic and immunologic responses in treatment-naive patients to ritonavir-boosted atazanavir or efavirenz with a common backbone. *HIV Clin Trials* 2014; **15**: 92–103.

**14** Rokx C, Fibriani A, van de Vijver D. Increased virological failure in naive HIV-1-infected patients taking lamivudine compared with emtricitabine in combination with tenofovir and efavirenz or nevirapine in the Dutch Nationwide ATHENA Cohort. *Clin Infect Dis* 2014; **60**: 143–53.

**15** Swiss HIV Cohort Study, Schoeni-Affolter F, Ledergerber B *et al*. Cohort profile: the Swiss HIV Cohort study. *Int J Epidemiol* 2010; **39**: 1179–89.

**16** Ledergerber B, Egger M, Opravil M *et al*. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. *Lancet* 1999; **353**: 863–8.

**17** Yerly S, Kaiser L, Race E *et al*. Transmission of antiretroviral-drug-resistant HIV-1 variants. *Lancet* 1999; **354**: 729–33.

**18** Wyl von V, Yerly S, Böni J *et al*. Emergence of HIV-1 drug resistance in previously untreated patients initiating combination antiretroviral treatment: a comparison of different regimen types. *Arch Intern Med* 2007; **167**: 1782–90.

**19** Johnson VA, Calvez V, Günthard HF *et al*. Update of the drug resistance mutations in HIV-1: March 2013. *Top Antivir Med* 2013; **21**: 6–14.

**20** Nachega JB, Parienti J-J, Uthman OA *et al*. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis* 2014; **58**: 1297–307.

**21** Blanco JL, Montaner JSG, Marconi VC *et al*. Lower prevalence of drug resistance mutations at first-line virological failure to first-line therapy with Atripla vs. tenofovir+emtricitabine/lamivudine+efavirenz administered on a multiple tablet therapy. *AIDS* 2014; **28**: 2531–9.

**22** Lennox JL, Landovitz RJ, Ribaudo HJ *et al*. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med* 2014; **161**: 461–71.

**23** Staehelin C, Keiser O, Calmy A *et al*. Longer term clinical and virological outcome of sub-Saharan African participants on antiretroviral treatment in the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr Hum Retrovirol* 2012; **59**: 79–85.

**24** Glass TR, Battegay M, Cavassini M *et al*. Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr Hum Retrovirol* 2010; **54**: 197–203.

**25** Scherrer AU, Ledergerber B, von Wyl V *et al*. Improved virological outcome in white patients infected with HIV-1 non-b subtypes compared to subtype B. *Clin Infect Dis* 2011; **53**: 1143–52.