Nevirapine in HIV maintenance therapy – can "old drugs" survive in current HIV management?

Notter Julia[a]**, Bregenzer Andrea**[ab]**, Vernazza Pietro**[a]**, Kahlert Christian R.**[ac]

[a] Cantonal Hospital St Gallen, Department of Infectious Diseases and Hospital Epidemiology, St Gallen, Switzerland
[b] Department of Infectious Diseases and Hospital Hygiene, Cantonal Hospital Aarau, Switzerland
[c] Children's Hospital of Eastern Switzerland, Department of Infectious Diseases and Hospital Epidemiology, St Gallen, Switzerland

Summary

AIMS OF THE STUDY: Nevirapine has an exceptional record for long-term tolerability with few side effects in human immunodeficiency virus (HIV) combined antiretroviral therapy (cART). Owing to relatively frequent hypersensitivity reactions (HSR) (15–25%) in the first 3 months after treatment initiation (especially in patients with a high CD4 count (>250/µl in women, >400/µl in men)), it is being used less and less. However, the rate of adverse events is lower when patients are already under suppressive cART. We present the results of a single centre strategy to offer the switch to a nevirapine-containing regimen and evaluate the potential role nevirapine could play in current antiretroviral treatment.

METHODS: All adult HIV-positive patients starting nevirapine at our centre since 2010 were evaluated in this retrospective analysis. We examined the proportion of patients on cART containing nevirapine, as well as the number of starts and stops every 6 months. Nevirapine discontinuation rates were analysed by sex, age, hepatitis C virus (HCV) status, time on nevirapine, ethnicity, CD4 nadir as well as CD4 count, HIV-RNA and ART backbone at nevirapine start.

RESULTS: Since 2014, more than a third of our treated HIV patients have been on nevirapine-containing therapy, with a stable percentage in the following years; 277 patients starting nevirapine for the first time were analysed. Thirty-three percent (92/277) of these first nevirapine therapies were discontinued, with 16 cases (17%) resuming nevirapine later during follow-up. Of the patients who continued nevirapine for more than 90 days (n = 221), 80% maintained nevirapine until their last follow-up. The nevirapine stop rate after the first 90 days was 15-fold lower (5.4 per 100 patient years, 95% confidence interval [CI] 4.0–7.2) than in the first 90 days. Overall, nevirapine was used for a median of 2.9 years (interquartile range [IQR] 0.5–5.6). In HCV co-infected patients, the treatment stop rate was 4-fold higher than in HIV mono-infected patients, but this difference was mainly due to treatment interruptions caused by drug-drug interactions with intermittent HCV therapy. Six out of seven Asian patients experienced HSR (hepatotoxicity / skin rash). In a population with 74%

3TC/ABC backbone, 81% fully suppressed, median CD4 nadir 240/µl (IQR 120–360) and median CD4 count at nevirapine start 590/µl (IQR 400–840), both high CD4 nadir and high CD4 count at nevirapine start were associated with lower rather than higher discontinuation rates. In fully suppressed patients with high CD4 count at nevirapine start, high CD4 nadir was not a risk factor for HSR. Major reasons for the discontinuation of nevirapine were HSR (liver, skin rash) in 38 cases (41% of all discontinuations) followed by other adverse drug reactions (n = 17) and non-adherence (n = 14). In patients who stopped nevirapine after more than 90 days, the major cause was non-adherence or other adverse drug reaction (both n = 12).

CONCLUSIONS: In this study, two thirds of the patients continued nevirapine with favourable long-term tolerability and efficacy. Thus, this low-cost "old drug" may still represent a valid treatment switch option for maintenance therapy in selected patients with a fully suppressed viral load. However, further evaluation is needed.

Keywords: infectious diseases, HIV, cART, HIV maintenance therapy, nevirapine

Background

Combined antiretroviral treatment (cART) with three antiretroviral compounds was established in 1996 and is able to achieve a complete and continued suppression of human immunodeficiency virus (HIV) replication within the body. The main reason to combine three compounds to treat HIV infection is to prevent the escape of drug resistant mutants. This risk is especially high during the initial phase of first-line therapy, when massive viral replication occurs. Once the virus is suppressed, no further viral replication and evolution occurs as long as the treatment is maintained [1]. As a result, life expectancy in people living with HIV is now similar to that of the general population [2]. All international guidelines specify antiretroviral combinations to initiate cART [3]. However, the distinct requirements of long-term maintenance therapy once viral replication has been stably suppressed has not been studied intensively. The most important requirement during the maintenance phase is to sustain viral suppression using compounds with as few as possible long-term side effects.

Nevirapine, the first NNRTI (non-nucleoside reverse transcriptase inhibitor), which entered the market in the early 1990s, is started less and less, but still continued today, and thus has an exceptional record for long-term tolerability [4–6]. Typical side effects of all NNRTIs include rash and hepatitis, as well as neuropsychological side effects and dyslipidaemia with efavirenz and rilpivirine. Dyslipidaemia, nausea and diarrhoea are frequent side effects of protease inhibitors. Among all the NNRTIs and protease inhibitors, nevirapine is the only one that has no negative effect on lipids [7]. One outstanding characteristic of nevirapine is its high penetration into sanctuaries. Among all antiretroviral drugs, nevirapine is probably the one with the best documented penetration rate in the genital tract and in the central nervous system including the brain tissue, and the drug is used with excellent results in HIV encephalopathy / HIV dementia [8, 9]. Additionally, it has been shown to be strongly correlated to undetectable HIV-DNA concentrations [10].

The reason, why nevirapine is not frequently started anymore despite its favourable price (see below) is the relatively frequent (15–25%) occurrence of hypersensitivity reactions (either skin rash or elevated liver enzymes) in the first 3 months after treatment initiation, especially in patients with a high CD4 count (>250/µl in women and >400/µl in men) [11, 12]. Undetected elevation of liver enzymes may cause liver failure during continued treatment with nevirapine. Interestingly, the rate of adverse events in HIV-positive individuals initiating nevirapine is lower if they are already under a suppressing antiretroviral regimen [13, 14].

On the basis of the latter observation, we started to evaluate the use of nevirapine for antiviral maintenance therapy at our centre, the infectious diseases clinic of the Cantonal Hospital St Gallen. Since 2010, we have systematically evaluated the option to switch patients on stable antiretroviral therapy to a nevirapine-containing regimen, including patients with high CD4 cell counts. As a consequence, nevirapine is now the most frequently used third agent in our centre, with more than 200 patients on nevirapine.

Within the Swiss HIV Cohort Study (SHCS) [15], a multicentre prospective observational study initiated in 1988, more than 850 patients are stably treated with nevirapine-containing regimens. Compared with the drug costs for the ten most common antiretroviral combinations used in the SHCS in 2017, nevirapine-based therapies are on average 22% or 300 CHF/month less expensive than the average costs of the other cART regimens.

Based on a retrospective chart review, we explored whether switching to a nevirapine-containing regimen could represent an option for maintenance therapy in current HIV management.

Methods

Study population and data collection
The Infectious Diseases Clinic of the Cantonal Hospital St Gallen is one of seven centres of the Swiss HIV Cohort Study (SHCS) and is the biggest non-university centre. It has a catchment area of about 600,000 people. The majority of Swiss HIV patients are treated at one of the SHCS centres, with the rest being treated at infectious disease units at smaller hospitals or in private practice. All adult HIV-infected patients followed up at the Infectious Diseases Clinic of the Cantonal Hospital St Gallen between 2010 and 2018 were considered for the analysis. Of these, all patients on a nevirapine-containing regimen were included in the analysis. Data in the clinical database were collected prospectively according to the standard defined by the SHCS [15]. The initial dose of nevirapine was 200 mg once daily, with an increase to one 400-mg prolonged release tablet daily after 2 weeks if there was no sign of adverse drug effects (e.g., rash, elevated liver enzymes). All treatment starts and stops were evaluated, and reasons for treatment interruption were obtained from chart review. This study was approved by the local ethics committee (Ethikkommission Ostschweiz, Project-ID 2018-01595).

Definitions
Hypersensitivity reaction (HSR) was defined as any rash or elevation of liver enzymes within the first 90 days of nevirapine treatment that led to nevirapine stop. *Nevirapine interruption* was defined as nevirapine stop followed by restart within the study period. A CD4+ lymphocyte count of >250/µl in females and >400/µl in males was considered as a "high CD4 count" and a CD4 count of ≤250/µl in females and ≤400/µl in males as "low CD4 count". *Undetectable viraemia* was defined as plasma HIV-RNA <50 copies/ml.

Statistical analyses
Descriptive statistics were used to characterise the study population.

Every 6 months between 2010 and 2018 (1 January and 1 July of each year), we determined the total number of patients on ART and nevirapine, the proportion of ART patients a on nevirapine-containing regimen and the number of nevirapine starts and stops in the past 6 months.

For the time-to-event analysis, we used only the first nevirapine treatment in each patient. Follow-up time was defined as time between nevirapine start and nevirapine stop. For patients in whom nevirapine was not stopped, follow-up time was censored at the date of last information (the latest of the following four dates: last follow-up date, last laboratory date, latest date on which the patient was known to be alive or date of death).

To calculate stop rates, the number of stops was divided by the total number of person-years. Associations between sex, age at nevirapine-start, hepatitis C virus (HCV) co-infection, time on nevirapine, ethnicity, CD4 nadir, CD4 cell count, HIV viral load and ART backbone at nevirapine start and stop rate were evaluated by calculation of rate ratios. Stop rates were considered significantly different at the 5% level, if the 95% confidence interval (CI) of the stop ratio did not include 1.

To investigate the effect of time under nevirapine on the stop rate, Lexis expansion was used. The Lexis expansion is a method that splits the follow-up time of individuals in a cohort study. Using this manipulation of cohort data, we can examine the effect of variables that change over time [16]. For each individual, the time on nevirapine was split into ≤90 days and >90 days, since hypersensitivity reactions to nevirapine usually occur within the first 90 days of therapy. Thus, separate stop rates for the first 90 days

on nevirapine and thereafter could be calculated and compared.

Kaplan-Meier survival curves for the probability of remaining on nevirapine, stratified by sex, age at nevirapine start (<45 years versus ≥45 years), HCV co-infection, ethnicity, CD4 nadir, CD4 count, HIV-RNA and ART backbone at nevirapine-start were compared using log-rank tests.

Stata Version 12.0 was used for statistical analyses.

Results

In 2010, 10% (39/379) of all HIV-patients treated at our clinic in St Gallen were on a nevirapine-containing regimen. By 2014, this number had increased to 33% (156/509). Since then, the percentage of patients treated with nevirapine remained stable at one third of the total number of patients treated, with 35% (192/544) in 2018 (fig.1).

Between 1 January 2010 and 31 July 2018, there were 307 nevirapine starts. In 277 cases, it was the first nevirapine start for that patient, in 26 the second, in 3 the third and in 1 the fourth. Thirty-three percent (101/307) of the nevirapine therapies were stopped during follow up; 19% (19/101) of the stops were actually interruptions and nevirapine was restarted at a later time-point during follow up. Baseline characteristics of 277 patients with a first nevirapine-containing cART are summarised in table 1.

Total observation time was 878 years (mean 3.2 years per patient), with the longest observation period of 8.2 years. Thirty-three percent (92/277) of first nevirapine therapies were discontinued; 17% (16/92) of these patients resumed nevirapine later during follow up. Sixty-seven percent (185/277) maintained nevirapine until their last contact with us. Overall, nevirapine was used for a median of 2.9 years with an interquartile range (IQR) of 0.5–5.6 years.

Of patients who continued nevirapine for more than 90 days (n = 221), the total observation time was 819 years (an average of 3.7 years per patient), with the longest observation period of 7.9 years. Twenty percent (44/221) discontinued nevirapine, of whom 32% (14/44) resumed it

later during follow up. Eighty percent (177/221) maintained nevirapine until their last contact with us. Overall, nevirapine-therapies that were continued for more than 90 days were used for a median of 4.2 years (IQR 1.5–5.9).

The nevirapine stop rate in the 277 patients with a first nevirapine therapy was 10.5/100 person years (95% CI 8.5–12.9) (table 2). Nevirapine stop rates in women and men were comparable. There was also no difference between patients starting their first nevirapine therapy at the age of ≥45 versus <45 years. However, the nevirapine stop rate was almost three times higher in HCV co-infected than in HIV mono-infected patients, and 15-fold higher during the first 90 days of nevirapine-containing cART than thereafter; 52% of nevirapine stops (48/92) occurred in the first 90 days of the treatment.

In the analysis of nevirapine therapies with a duration of >90 days (n = 221), the overall stop rate was reduced to 5.4/100 person years (table 2B). Again, there was no difference between women and men, and age ≥45 and <45 years at nevirapine start, but the nevirapine stop rate in HCV co-infected was 4-fold higher than in HIV-mono-infected patients.

Six out of seven Asian patients experienced HSR (hepatotoxicity / skin rash) within the first month after nevirapine-start. Among all HSR cases, patients with a CD4 count ≥350 and <500/µl at nevirapine start were overrepresented (32% [12/38] vs 18% [42/237], p = 0.046). At 4.3% (2/46), the proportion with HSR was lowest in patients with CD4 count <350/µl at nevirapine start. It was higher in patients with a CD4 count ≥500/µl (13.7% [24/175], p = 0.079), and highest in patients with CD4 count ≥200 and <350/µl at nevirapine start (22.2% [12/54], p = 0.010). In fully suppressed patients with high CD4 counts at nevirapine start, a high CD4 nadir was not a risk factor for HSR. Overall, 9.4% (5/53) of patients classified as "high-high-undetectable" versus 17.7% (23/130) of patients classified as "low-high-undetectable" experienced HSR (p = 0.159). The overall nevirapine discontinuation rate was also lower in the "high-high-undetectable" group (fig. 2).

Figure 1: Percentage of patients on nevirapine (NVP)-containing HIV therapy.
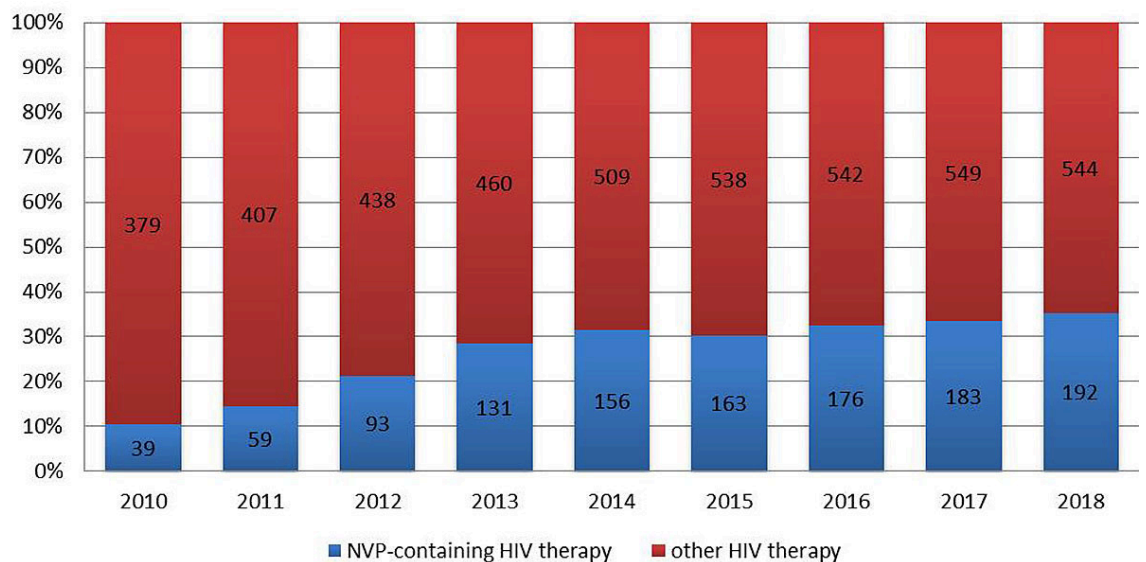
In a population with 74% lamivudine/abacavir backbone, 81% fully suppressed, median CD4 nadir 240/µl (IQR 120–360) and median CD4-count at nevirapine start 590/µl (IQR 400–840) (refer to the baseline characteristics, table 1), both high CD4 nadir and high CD4 count at nevirapine start were associated with lower rather than higher discontinuation rates (figs 3 and 4, table 2).

Major reasons for the 92 discontinuations of nevirapine were: hypersensitivity reactions during the first 90 days (liver toxicity and/or skin rash) in 38 cases (41%) after a median time on nevirapine of 28 days (IQR 17–44, ange 1–81 days); other adverse drug reactions in 17 cases (19%); and non-adherence in 14 (15%). Detailed reasons are listed in table 3. Notably, five patients died while on nevirapine therapy. None of the five deaths was associated

Table 1: Baseline characteristics of patients using nevirapine.

			All first NVP therapies since 1 Jan 2010 (n = 277; 92 stops)	Duration ≤90 days (n = 56; 48 stops)	Duration >90 days (n = 221; 44 stops)
Sex	Female		24% (66)	20% (11)	25% (55)
	Male		76% (211)	80% (45)	75% (166)
Age (y)	Median (IQR)		47 (38–54)	48 (38–56)	47 (38–53)
	<45		43% (119)	34% (19)	45% (100)
	≥45		57% (158)	66% (37)	55% (121)
Ethnicity	White		85% (235)	82% (46)	86% (189)
	Black		12% (32)	7% (4)	13% (28)
	Hispanic		1% (3)	0% (0)	1% (3)
	Asian		3% (7)	11% (6)	0.5% (1)
HCV co-infection			18% (50)	21% (12)	17% (38)
CD4 nadir (…/µl)	Median (IQR)	All	240 (120–360)	220 (145–340)	240 (120-360)
		Women	212 (110–320)	220 (110–420)	210 (109-320)
		Men	240 (140–380)	220 (153–310)	240 (130-390)
	<200		39% (109)	39% (22)	39% (87)
	≥200 and <350		34% (94)	36% (20)	33% (74)
	≥350 and <500		16% (45)	14% (8)	17% (37)
	≥500		10% (29)	11% (6)	10% (23)
	Low*		75% (208)	80% (45)	74% (163)
	High†		25% (69)	20% (11)	26% (58)
CD4 at NVP start (…/µl)	Median (IQR)	All	590 (400–840) (n = 275)	585 (415–753) (n = 56)	590 (380-870) (n = 219)
		Women	620 (380–860) (n = 65)	755 (600–1060) (n = 11)	585 (370-820) (n = 54)
		Men	580 (400–840) (n = 210)	540 (410–730) (n = 45)	590 (400-890) (n = 165)
	<200		5% (14/275)	4% (2/56)	5% (12/219)
	≥200 and <350		12% (32/275)	5% (3/56)	13% (29/219)
	≥350 and <500		20% (54/275)	29% (16/56)	17% (38/219)
	≥500		62% (175/275)	63% (35/56)	64% (140/219)
	Low*		22% (61/275)	20% (11/56)	23% (50/219)
	High†		78% (214/275)	80% (45/56)	77% (169/219)
HIV-RNA (cop/ml)	<50		81% (223/275)	86% (48)	80% (175/219)
	≥50		19% (52/275)	14% (8)	20% (44/219)
	Low-low-detectable		8% (21/275)	9% (5/56)	7% (16/219)
	Low-low-undetectable		15% (40/275)	11% (6/56)	16% (34/219)
	Low-high-detectable		6% (16/275)	2% (1/56)	7% (15/219)
	Low-high-undetectable		47% (130/275)	59% (33/56)	44% (97/219)
	High-high-detectable		5% (15/275)	4% (2/56)	6% (13/219)
	High-high-undetectable		19% (53/275)	16% (9/56)	20% (44/219)
NVP-start	2010–2011		28% (77)	21% (12)	29% (65)
	2012–2013		34% (93)	29% (16)	35% (77)
	2014–2015		17% (48)	23% (13)	16% (35)
	2016–2017		17% (47)	7% (4)	19% (43)
	01–07/2018		4% (12)	20% (11)	0.5% (1)
Backbone at NVP start	3TC/ABC		74% (204)	79% (44)	72% (160)
	ETC/TDF		21% (59)	16% (9)	23% (50)
	ETC/TAF		2% (6)	4% (2)	2% (4)
	3TC/TDF		1% (3)	0% (0)	1% (3)
	Other		2% (5)	2% (1)	2% (4)

3TC = lamivudine; ABC = abacavir; ETC = emtricitabine; IQR = interquartile range; NVP = nevirapine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate * ≤250/µl in women and ≤400/µl in men † >250/µl in women and ≥400/µl in men "Low/high-low/high-detectable/undetectable" refers to "(CD4 nadir)–(CD4 at NVP-start)–(HIV RNA at NVP start)" with "low" for CD4 ≤250/µl in women and ≤400/µl in men, "high" for CD4 >250/µl in women and >400/µl in men, "detectable" for HIV-RNA ≥50 cop/ml and "undetectable" for HIV-RNA <50 cop/ml

Table 2: Nevirapine stop rates in all nevirapine first therapies by sex, age, HCV-serostatus and duration on nevirapine.

		Stops (n)	FU time (y)	Stop rate (per 100 PY) (95% CI)	Crude rate ratio (95% CI)	p-value
(A) All patients on NVP (n = 277)						
Overall		92	878.1	10.5 (8.5–12.9)	–	–
Sex	Men	69	653.9	10.6 (8.3–13.4)	1.00 (ref.)	0.907
	Women	23	224.2	10.3 (6.8–15.4)	0.97 (0.61–1.56)	
Age at NVP start	<45 years	39	376.4	10.4 (7.6–14.2)	1.0 (ref.)	0.927
	≥45 years	53	501.6	10.6 (8.1–13.8)	1.02 (0.67–1.54)	
HCV status	Negative	63	757.3	8.3 (6.5–10.6)	1.00 (ref.)	<0.001
	Positive	29	120.7	24.0 (16.7–34.6)	2.89 (1.86–4.48)	
Days on NVP	≤90	48	59.4	80.8 (60.9–107.3)	1.00 (ref.)	<0.001
	>90	44	818.6	5.4 (4.0–7.2)	0.066 (0.044–0.100)	
Ethnicity – all	White	75	769.6	9.7 (7.8–12.2)	1.00 (ref.)	
	Black	11	88.6	12.4 (6.9–22.4)	1.27 (0.68–2.40)	0.452
	Hispanic	0	14.5	0	0.00	0.235
	Asian	6	5.4	111.5 (50.1–248.1)	11.44 (4.98–26.27)	<0.001
Ethnicity – non-Asian vs Asian	Non–Asian	86	872.6	9.9 (8.0–12.2)	1.00 (ref.)	<0.001
	Asian	6	5.4	111.5 (50.1–248.1)	11.31 (4.94–25.88)	
CD4 nadir (…/µl)	<200	45	318.3	14.1 (10.6–18.9)	1.00 (ref.)	0.012
	≥200	47	559.7	8.4 (6.3–11.2)	0.59 (0.34–0.89)	
High CD4 nadir[*]	No	75	648.5	11.6 (9.2–14.5)	1.00 (ref.)	0.095
	Yes	17	229.5	7.4 (4.6–11.9)	0.64 (0.38–1.08)	
High CD4 at NVP start[*]	No	26	171.0	15.2 (10.3–22.3)	1.00 (ref.)	0.030
	Yes	65	922.9	9.2 (7.2–11.8)	0.61 (0.39–0.96)	
HIV-RNA (cop/ml)	<50	72	709.1	10.2 (8.1–12.8)	1.00 (ref.)	0.646
	≥50	19	166.3	11.4 (7.3–17.9)	1.13 (0.68–1.87)	
	Low–low–detectable	12	40.5	29.7 (16.8–52.2)	2.50 (1.32–4.70)	0.003
	Low–low–undetectable	14	130.6	10.7 (6.4–18.1)	0.90 (0.50–1.64)	0.735
	Low–high–detectable	2	81.4	2.5 (0.6–9.8)	0.21 (0.05–0.85)	0.016
	Low–high–undetectable	47	395.5	11.9 (8.9–15.8)	1.00 (ref.)	0.908
	High–high–detectable	5	44.4	11.3 (4.7–27.0)	0.95 (0.38–2.38)	0.038
	High–high–undetectable	11	183.1	6.0 (3.3–10.9)	0.51 (0.26–0.98)	0.003
3TC/ABC-backbone at NVP start	Yes	68	648.2	10.5 (8.3–13.3)	1.00 (ref.)	0.985
	No	24	229.8	10.4 (7.0–15.6)	1.00 (0.63–1.59)	
(B) Patients who were on NVP >90 days (n = 221)						
Overall		44	818.6	5.4 (4.0–7.2)	–	–
Sex	Men	30	608.8	4.9 (3.4–7.0)	1.00 (ref.)	0.347
	Women	14	209.8	6.7 (4.0–11.3)	1.35 (0.72–2.55)	
Age at NVP start	<45 years	22	350.4	6.3 (4.1–9.5)	1.00 (ref.)	0.335
	≥45 years	22	468.2	4.7 (3.1–7.1)	0.75 (0.42–1.35)	
HCV status	Negative	27	708.4	3.8 (2.6–5.6)	1.00 (ref.)	<0.001
	Positive	17	110.3	15.4 (9.6–24.8)	4.04 (2.20–7.42)	
Ethnicity	White	36	718.8	5.0 (3.6–6.9)	1.00 (ref.)	
	Black	8	81.3	9.8 (4.9–19.7)	1.97 (0.91–4.23)	0.078
	Hispanic	0	13.7	0.0	0.00	0.407
	Asian	0	4.9	0.0	0.00	0.621
	Non–Asian	44	813.8	5.4 (4.0–7.3)	1.00 (ref.)	0.608
	Asian	0	4.9	0.0	0.00	
CD4 nadir (…/µl)	<200	25	295.0	8.5 (5.7–12.5)	1.00 (ref.)	0.004
	≥200	19	523.6	3.6 (2.3–5.7)	0.43 (0.24–0.78)	
High CD4 nadir[*]	No	35	604.3	5.8 (4.2–8.1)	1.00 (ref.)	0.388
	Yes	9	214.3	4.2 (2.2–8.1)	0.73 (0.35–1.51)	
High CD4 at NVP start[*]	No	16	157.9	10.1 (6.2–16.5)	1.00 (ref.)	0.003
	Yes	27	658.6	4.1 (2.8–6.0)	0.40 (0.22–0.75)	
HIV-RNA (cop/ml)	<50	31	661.6	4.7 (3.3–6.7)	1.00 (ref.)	0.135
	≥50	12	154.8	7.8 (4.4–13.6)	1.65 (0.85–3.22)	
	Low–low–detectable	8	36.2	22.1 (11.1–44.2)	4.53 (1.97–10.41)	
	Low–low–undetectable	8	121.7	6.8 (3.3–13.1)	1.35 (0.59–3.10)	<0.001
	Low–high–detectable	1	77.6	1.3 (0.2–9.1)	0.26 (0.04–1.98)	0.483
	Low–high–undetectable	18	368.5	4.9 (3.1–7.8)	1.00 (ref.)	0.163
	High–high–detectable	3	41.1	7.3 (2.4–22.7)	1.50 (0.44–5.08)	0.516
	High–high–undetectable	5	171.5	2.9 (1.2–7.0)	0.56 (0.22–1.61)	0.302

		Stops (n)	FU time (y)	Stop rate (per 100 PY) (95% CI)	Crude rate ratio (95% CI)	p-value
3TC/ABC backbone at NVP-start	Yes	31	604.8	5.1 (3.6–7.3)	1.00 (ref.)	0.605
	No	13	213.9	6.1 (3.5–10.5)	1.19 (0.62–2.27)	

NVP = nevirapine; 3TC = lamivudine; ABC = abacavir; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; FU = follow-up; PY = person years; CI = confidence interval; ref. = reference * >250/µl in women and >400/µl in men "Low/high-low/high-detectable/undetectable" refers to "(CD4 nadir)–(CD4 at NVP start)–(HIV-RNA at NVP start)" with "low" for CD4 ≤250/µl in women and ≤400/µl in men, "high" for CD4 >250/µl in women and >400/µl in men, "detectable" for HIV-RNA ≥50 cop/ml and "undetectable" for HIV-RNA <50 cop/ml.

with a known adverse effect of nevirapine. Causes of death were myocardial infarction (two), drug overdose (one), oropharyngeal carcinoma (one) and pneumonia with respiratory failure (one); four of the five patients were co-infected with HCV.

For the 44 patients who stopped nevirapine after more than 90 days, major reasons were: non-adherence in 12 cases (27%), including two patients with low-level viraemia; and "other adverse drug reactions" in another 12 (27%). Additionally, three patients had elevated liver enzymes and two a skin rash. However, according to the chart review, these adverse events were mild and not clearly associated with nevirapine. In 4 of the 50 (9%) patients co-infected with HCV, therapy was stopped due to interactions with

Figure 2: Kaplan-Meier survival curves: probability of remaining on nevirapine (NVP) in high-high-undetectable patients versus low-high-undetectable patients. "Low/high-low/high-detectable/undetectable" refers to "(CD4 nadir)–(CD4 at NVP start)–(HIV-RNA at NVP start)" with "low" for CD4 ≤250/µl in women and ≤400/µl in men, "high" for CD4 >250/µl in women and >400/µl in men, "detectable" for HIV-RNA ≥50 cop/ml and "undetectable" for HIV-RNA <50 cop/ml.
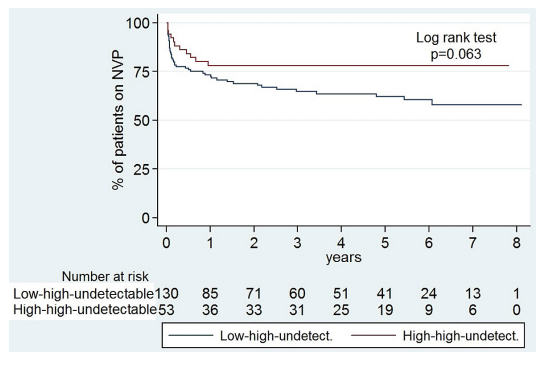
Figure 3: Kaplan-Meier survival curves: probability of remaining on nevirapine (NVP) with high CD4 at NVP start versus low CD4 at NVP start.
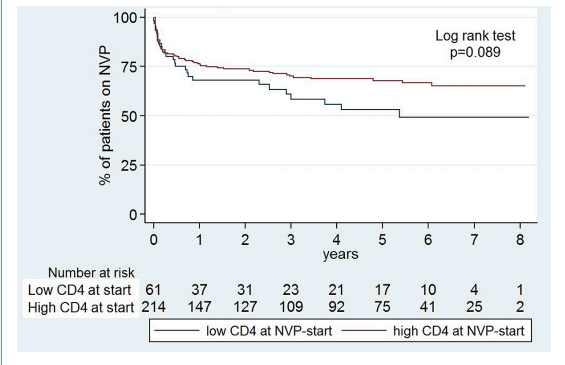
Table 3: Reasons for stopping or interrupting nevirapine therapies (after 1 Jan 2010).

(A) All Nevirapine stops (n = 92/277, 33%)			
	All (n = 92) interruptions: 17% (16)	HCV-negative (n = 63) interruptions: 16% (10)	HCV-positive (n = 29) interruptions: 21% (6)
Hypersensitivity reaction*	41% (38)	51% (32)	21% (6)
Other adverse drug reaction†	19% (17)	16% (10)	24% (7)
Non-Adherence	15% (14)	14% (9)	17% (5)
Skin rash or elevated liver enzymes‡	5% (5)	5% (3)	7% (2)
Interaction HCV therapy	4% (4)	0% (0)	14% (4)
Other interaction§	2% (2)	2% (1)	3% (1)
Patient's wish	4% (4)	6% (4)	0% (0)
Interruption of insurance coverage	1% (1)	2% (1)	0% (0)
Death	5% (5)	2% (1)¶	14% (4)‖
Drop-out	2% (2)	3% (2)	0% (0)
(B) Nevirapine-stops after 90 days of therapy (n = 44/221, 20%)			
	All (n = 44) interruptions: 32% (14)	HCV-negative (n = 27) interruptions: 33% (9)	HCV-positive (n = 17) Interruptions: 29% (5)
Skin rash or elevated liver enzymes‡	11% (5)	11% (3)	12% (2)
Other adverse drug reaction†	27% (12)	30% (8)	24% (4)
Non-adherence	27% (12)	33% (9)	18% (3)
Interaction HCV therapy	9% (4)	0% (0)	24% (4)
Other interaction§	2% (1)	4% (1)	0% (0)
Patient's wish	7% (3)	11% (3)	0% (0)
Interruption of insurance coverage	2% (1)	4% (1)	0% (0)
Death	9% (4)	0% (0)	24% (4)‖
Drop-out	5% (2)	7% (2)	0% (0)

* Skin rash and/or elevated liver enzymes including the 5 patients in part 2 specified as "skin rash or elevated liver enzymes" † Other than hypersensitivity reactions ‡ Not clearly associated with nevirapine use: 3 cases had elevated liver enzymes, 2 cases of intercurrent skin rash § For example, chemotherapy, methadone ¶ Myocardial infarction ‖ Myocardial infarction, oropharyngeal carcinoma, pneumonia, probable drug overdose

a planned Hepatitis C-therapy. In a Kaplan-Meier analysis (fig. 5), the probability of remaining on the first nevirapine therapy was significantly higher in HIV mono-infected patients compared to HIV-HCV co-infected patients.

Discussion

This retrospective study examined the potential of nevirapine as a switch option for maintenance therapy in our cohort of HIV patients. A switch to nevirapine was offered after reaching stable viral suppression and included patients with high CD4 counts (>250/µl in women and >400/µl in men) both before ART and at nevirapine start (high-high-undetectable), which is a growing population since nowadays ART is recommended irrespective of CD4 count [17]. Overall, 38/277 patients (14%) had to discontinue nevirapine because of HSR, which is within the expected range known from previous studies [11, 12]. Liver enzyme elevations or skin rashes observed after 90 days of nevirapine use were mild and could not clearly be associated with the therapy. There was no significant difference between stop rates of male and female patients, even though previous results from the ATHENA cohort in patients starting nevirapine as first-line cART demonstrated female sex to be a risk factor for nevirapine associated HSR [13]. In accordance with the results of this latter study, 6/7 of our patients from Asia experienced HSR, which indicates Asian ethnicity is a risk factor. Remarkably, they also observed that in ART-experienced patients with an undetectable viral load and a high CD4 count at nevirapine start, a high CD4 count before ART significantly increased the HSR risk

from 5.2% (31/596) to 9.3% (24/258) (p = 0.025). In contrast, our results do not suggest such a difference, with a HSR prevalence of 17.7% (23/130) in the low-high-undetectable and 9.4% (5/53) in the high-high-undetectable group (p = 0.159). The higher HSR prevalence in our population (overall 38/277, 14%) might be in part due to the fact that three quarters of the patients had lamivudine/abacavir as ART backbone compared with only ≤11% in earlier studies, where zidovudine/abacavir was still dominating [13, 18]. Thus, abacavir-related hypersensitivity might have been misclassified as HSR due to nevirapine, unless patients had a screening test for the HLA-B*5701 allele prior to treatment start [19]. Another difference between the study populations is that in our study, the median CD4 count at nevirapine start was >500/µl, whereas it was only 350–400/µl in the ATHENA study. This is of note because in our study patients with HSR had more often CD4 counts at nevirapine start of between 350/µl and 500/µl.
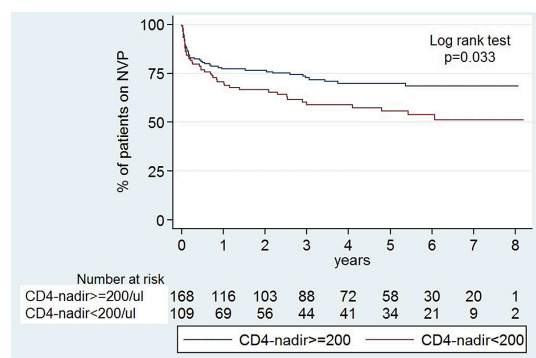
Inarguably, nevirapine has the potential for severe side effects and starting nevirapine therapy requires close follow up, especially during the first 3 months as the majority of hypersensitivity reactions occur within this time-frame. However, for long-term use, nevirapine has an exceptional record of tolerability and few side effects, which makes it a good choice for cART maintenance. In the ATHENA cohort patients who switched their first-line highly active ART despite successful viral suppression, switching from a protease inhibitor to nevirapine while continuing the other antiretroviral drugs was associated with a risk of a subsequent toxicity-driven switch five-fold lower than changing to another protease inhibitor-containing regimen [5]. In patients of the French Nationwide Cohort Study who received stable antiretroviral regimens for at least 6 months, treatment discontinuation due to adverse events was two- to –three-fold lower with abacavir/lamivudine/nevirapine (97% given as a switch regimen) compared with other standard antiretroviral regimens before 2013 [20]. In EuroSIDA patients starting nevirapine-, efavirenz- or lopinavir-based cART for the first time, follow up started ≥3 months after initiation of treatment if HIV-RNA was <500 copies/ml. Compared with the nevirapine group, those on efavirenz had a 31% (p = 0.01) and those on lopinavir a 66% (p <0.0001) higher risk of discontinuation because of toxicities or patient/physician choice [5].

In general, the advantage of "old drugs" that have been used for many years are that potential side effects – especially rare events and those occurring after long-term exposure – are often better known as compared with "new drugs". Moreover, the drug costs are favourable.
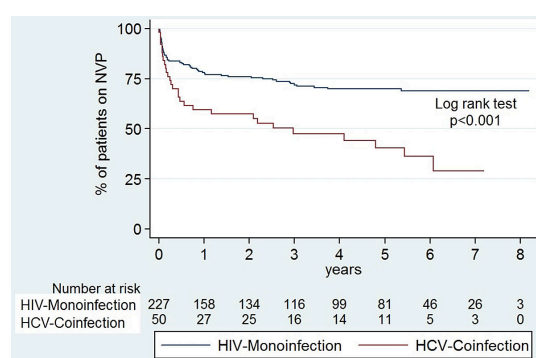
There were only two discontinuations of nevirapine due to low-level viraemia in our patients, with probable non-adherence in both cases. Importantly, we did not see an emergence of viral resistance. This is remarkable because nevirapine has a low barrier to resistance as it requires only a single mutation in the reverse transcriptase genome, as opposed to, for example, protease inhibitors, which generally require four to six mutations in the protease gene to develop viral failure, or integrase inhibitors. However, as argued in the Background section, this risk is highest in the initial phase of therapy when massive viral replication occurs.

As with most cART regimens, the most common reason for stopping nevirapine was poor adherence, which often

Figure 4: Kaplan-Meier survival curves: probability of remaining on nevirapine (NVP) with CD4 nadir ≥200/µl versus <200/µl.

Number at risk

	0	1	2	3	4	5	6	7	8
CD4-nadir>=200/ul	168	116	103	88	72	58	30	20	1
CD4-nadir<200/ul	109	69	56	44	41	34	21	9	2

Figure 5: Kaplan-Meier survival curves: probability of remaining on nervirapine (NVP) with hepatitis C virus (HCV) co-infection versus HIV monoinfection.

Number at risk

	0	1	2	3	4	5	6	7	8
HIV-Monoinfection	227	158	134	116	99	81	46	26	3
HCV-Coinfection	50	27	25	16	14	11	5	3	0

resulted in a complete ART stop. This may not be directly linked to nevirapine, but may rather be a general challenge in patients using ART. A cohort analysis in Sweden [21] showed discontinuation rates for efavirenz of 35% in ART-naïve patients and 44% in ART-experienced patients after 3 years. Although the discontinuation rate is similar in our study (33%), significantly fewer patients (20%) stopped nevirapine after more than 90 days, which supports the good tolerability and the occurrence of few long-term side effects once the risk period for hypersensitivity reaction has passed.

We found a significantly higher discontinuation rate in patients co-infected with HCV. However, hypersensitivity or other adverse drug reactions were not more frequent than in HIV mono-infected patients. The two main different reasons for nevirapine discontinuation in the co-infected group were interactions with a planned HCV therapy and death. Interactions with direct-acting antivirals (DAAs) for hepatitis C treatment that limit the use of nevirapine in co-infected patients has become an important consideration in recent years, especially since October 2017 when DAAs became more widely used. However, for patients switching to a different cART-regimen because of HCV therapy, switching back to a nevirapine-containing regimen after completion could be an option and was performed in two of our cases. Higher mortality of co-infected individuals has been described in the literature [22], similarly to the results in our cohort.

When switching to nevirapine, good patient instruction is vital, including the instruction to immediately contact the clinic in the case of pruritus or skin rash, and 2-weekly liver enzyme tests. The US Centers for Disease Control and Prevention (CDC) reviewed 22 reports of serious adverse events related to nevirapine taken for post-exposure prophylaxis after HIV exposure. Routine 2-weekly measurement of liver enzymes was not described in the review, and in six patients, a starting dose of 200 mg, as proposed for nevirapine, was not used [23]. In Stevens-Johnson syndrome and toxic epidermal necrolysis, prompt discontinuation of the causative agent is crucial to decrease mortality [24]. This underscores the importance of a proper follow up and good patient instruction. Thus, for the first 3 months, patients are required to comply with the somewhat time-consuming follow up, which is, however, feasible with properly motivated and informed patients.

This was a retrospective and monocentric analysis with inherent limitations. First, there is a selection bias, as patients with already elevated liver enzymes or poor adherence were probably not offered a switch to nevirapine-containing cART, which might have led to an overestimation of tolerability. Second, the design did not include a control group to compare tolerability to an alternative regimen. Third, we did not perform a multivariate analysis to investigate specific risk factors for stopping nevirapine. Fourth, the number of patients included did not allow any conclusion about the occurrence of rare severe side effects. Finally, we did not perform a cost-effectiveness analysis to compare the total of nevirapine-containing treatment costs to other cART regimens. As a result of these limitations, it is not possible to make any claim of superiority of a nevirapine-based regimen over any other cART. However, this is the largest cohort of nevirapine treated patients in a Swiss

HIV centre providing data on current efficacy and safety of a treatment alternative in current HIV management.

In conclusion, two third of the patients continued nevirapine with favourable long-term tolerability and efficacy. Thus, our results suggest that this low-cost "old drug" may still represent a valid switch option for maintenance therapy in selected patients with a fully suppressed viral load. Initial close follow-up ensures early detection of potential side effects and avoids irreversible adverse events in patients. Further evaluation is needed to confirm the results.

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