Virological failure and patterns of resistance-associated mutations in previously untreated HIV-positive participants in the RESINA cohort

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Introduction

The introduction of combination antiretroviral therapy (cART) significantly improved the clinical outcomes of people living with HIV (PLWH). Modern cART options have improved safety profiles, have fewer side effects and coupled with single-tablet regimens and long-acting formulations have enhanced adherence and quality of life for many patients. However, virologic failure (VF) still remains a concern, especially in PLWH who have developed resistance mutations under previous cART regimens. This study aimed to determine the frequencies and risk factors of VF and characterize the patterns of resistance mutations in a cohort of previously untreated HIV-positive participants of the RESINA cohort.

Methods

RESINA is a multicenter prospective cohort study examining the epidemiology of transmitted HIV drug resistance in North Rhine-Westphalia, Germany. We performed a descriptive analysis of study participants with VF, defined as an HIV-RNA above 200 copies/ml after an episode of viral suppression.
Since the 2nd generation protease inhibitor (PI) darunavir and the 1st generation integrase inhibitor (INI) raltegravir were approved in Germany during 2007 and the first 2nd generation INI dolutegravir was introduced in 2014, the incidence of VF was stratified into three groups according to the year of ART initiation: Group 1 from 2001-2007, Group 2 from 2008-2013 and Group 3: from 2014 onwards. Statistical analysis was performed using GraphPad Prism version 9 (GraphPad Software, Boston MA 02110).

Results

Frequency of VF:
From 2001 to 2022, 4983 participants were enrolled, of whom 103 experienced a VF (59/1368 [4.31%], 40/1835 [2.18%] and 4/1780 [0.22%] in groups 1-3 respectively.

Demographic and clinical parameters of participants with VF:

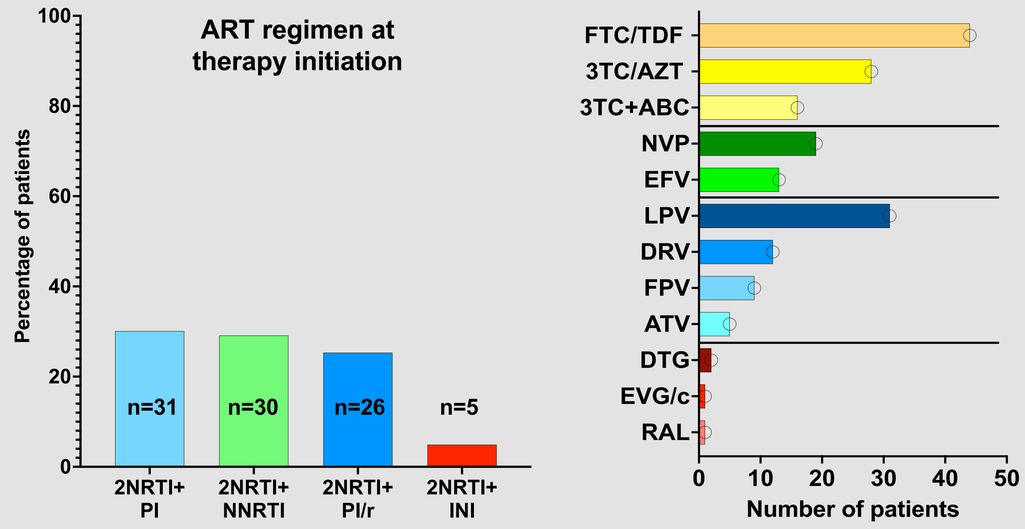
Age (median, range)	36 (22-69)
Gender (M/F)	65/38
Transmission route	
Heterosexual	28 (27.2 %)
Heterosexual from high prevalence country	21 (20.4 %)
MSM	29 (28.2%)
IDU	12 (11.7 %)
Other/unknown	13 (12.6 %)
Ethnicity	
German	59 (57.3 %)
European (other)	9 (8.7 %)
Sub-Saharan Africa	19 (18.4 %)
Asia	10 (9.7 %)
Other	6 (5.9 %)
Median CD4 (range) cells/µl	70 (1-460)
Median HIV1 RNA (range) at study inclusion copies/ml	76,708 (103-1418184)
HIV-1 Subtype	
B	59 (57.3 %)
CRF02_AG	15 (14.6 %)
C	5 (4.8 %)
Other	24 (23.3 %)
Late diagnosis (AIDS, Stage 3)	48 (46.6 %)

M. male, F: female; MSM: men who have ex with men; IDU: intravenous drug users

Risk factors for VF:
Non-adherence was documented as the reason for VF in 47 (45.6%) participants.

Results

ART regimens



NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor; r: ritonavir; FTC: emtricitabine, TDF: tenofovir; AZT: zidovudine; 3TC: lamivudine; ABC: abacavir; NVP: nevirapine; EFV: efavirenz; DRV: darunavir; LPV: lopinavir; FPV: fosamprenavir; ATV: atazanavir; DTG: dolutegravir; EVG/c: elvitegravir/cobicistat; RAL: raltegravir

At the time of VF, 52 (50.5%) participants were on their first ART-regimen, while 29 (28.2%) and 14 (13.6%) were on their 2nd and 3rd ART-regimen.

Pattern of resistance mutations
29 patients (28.2%) developed resistance-associated mutations, 21 of whom against ≥2 drug classes.

Most common Major Resistance Mutations

	Nr of patients
NRTI	Total= 22
M184 V/I	21
M41 L	2
T215 F	3
K70 R/E	2
K219 Q/E	2
NNRTI	Total=20
K101 E	6
K103 N	6
Y181	6

	Nr of patients
PI	Total= 4
V82A	3
N88NS	1
INI	Total=5
N155H	2
H51HY	1
E92EQ	1
Y143CPRS	1
R263K	1
G118R	1

Patients developing INI mutations: N155H, H51HY, E92Q and Y143CPRS were acquired by patients who failed under regimens containing RAL or EVG/c. R263K and G118R were quired by a patient who failed under dolutegravir.

Twenty-two people did not achieve subsequent viral suppression until the end of the follow-up period: 3 of them died and 13 were lost to follow-up; Eight of these patients had documented resistance mutations, two of which died. Five of these patients had no NNRTI and INI major mutations that could interfere with cabotegravir/rilpivirine (CBV/RPV) therapy, so this option could be used if non-adherence is considered to be an issue.

Conclusion

The frequency of VF decreased over time. Better tolerability and a high genetic barrier to resistance of the 2nd generation PIs and INIs are crucial for sustained viral suppression. Lack of treatment adherence remains one of the main causes of VF. CBV/RPV remains a therapeutic option in some patients with history of VF and could improve adherence.

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