The Role of Prior HBV Infection and Resistance Mutations on the Efficacy of 3TC/DTG as a Maintenance Therapy

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Article

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Abstract

Lamivudine/dolutegravir (3TC/DTG) is effective and safe for most people with HIV infection (PWH) who are virologically suppressed, but specific individual's characteristics, such as previous detection of archived resistance-associated mutations (RAMs) to 3TC and prior HBV infection, could represent a risk for virological failure (VF). We conducted a retrospective monocentric cohort study to assess rates and predictors of treatment discontinuation (TD) and VF in PWH switched to 3TC/DTG after reaching virological suppression (HIV-RNA<50 cp/mL). Overall, 188 PWH were included. Over 5145 patient-years follow-up (PYFU), 16 (8.5%) PWH experienced TD (2.87 per 1000 PYFU), whereas over 5082 PYFU, 8 (4.3%) experienced VF (1.45 per 1000 PYFU). Probabilities of TD and VF were 1.3%, 2.8%, 7.5%, 12.9%, 34.5% and 0.6%, 2.7%, 2.7%, 4.2%, 22.3% after 1, 2, 3, 4 and 5 years respectively. Independent predictors of VF were a detectable baseline HIV-RNA of 20-49 copies/ml (versus<20 copies/ml, aHR 9.11, 95 % CI 1.05-79.40; p= 0.046), and a higher GSS-score for 3TC (per 10 points more, aHR 1.57, 95 % CI 1.07-2.29; p= 0.023), with a borderline significance for anti-HBcAg positive serostatus (versus negative, aHR 8.88, 95 % CI 0.89-88.45; p= 0.062). After adjustment for age and gender, those with anti-HBcAg positivity who switched from a tenofovir-containing regimen had the highest risk of VF (versus negative anti-HBcAg and no prior tenofovir use, aHR 15.06, 95% CI 1.40-161.38; p-value= 0.025).

Keywords: HIV infection; antiretroviral therapy; occult HBV infection; dual ART; virological failure

1. Introduction

Dual antiretroviral (ART) regimen with dolutegravir (DTG) and lamivudine (3TC) represents a favourable option both as a first line regimen and as a simplification strategy in selected people living with Human Immunodeficiency Virus (PWH) [1]. For ART-naïve PWH, contraindications to this regimen are high viral load and previous failure with tenofovir/emtricitabine Pre-Exposure Prophylaxis (PrEP), while, for treatment experienced patients, 3TC/DTG should only be considered in PWH with no history of resistances to nucleoside reverse transcriptase inhibitors (NRTI) and/or integrase strand transfer inhibitors (INSTI) [1,2]. Current guidelines recommend against this regimen in case of Hepatitis B Virus (HBV) coinfection, defined by HBsAg-positivity, while isolated anti-HBcAg positivity, marker of a previous exposure to HBV infection, is not an absolute contraindication [3,4]. The synergistic effect of HIV and active HBV coinfection is widely recognized, and is characterized by worse immune recovery, higher rates of virological failures on ART, increased signs of chronic immune activation and more frequent undesirable HBV related outcomes [3–6]. Some authors have also been consistently describing worse control of HIV infection with 3TC/DTG

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in PWH with isolated anti-HBcAg positivity [3,4]. Due to conflicting data [7–15], the relevance of archived resistance associated mutations (RAMs) to 3TC on 3TC/DTG effectiveness is also debated.

Our goal was to assess rates and predictors of virological failure (VF) and treatment discontinuation (TD) with 3TC/DTG in our cohort of PWH, with particular focus on the role of resistance mutations and anti-HBcAg serostatus.

2. Materials and Methods

We conducted a retrospective cohort study in a 3rd level University hospital in Pisa, Italy. Adult (≥18 years-old) PWH on stable ART were considered eligible for study participation if they underwent a switch to 3TC/DTG after reaching virological suppression (HIV-RNA<50 copies/mL) from the 1st of January 2015 to 31st of December 2023. Exclusion criteria were a positive HBsAg serostatus, previous exposure to 3TC/DTG and lack of at least one follow-up measurement of serum HIV-RNA. The main study objectives were time to VF (defined as two consecutive HIV-RNA>50 copies/mL, a single HIV-RNA≥200 copies/mL, or a single HIV-RNA between 50 and 200 copies/mL followed by TD and regimen intensification) and time to TD for any cause. Predictors of VF were subsequently investigated, particularly considering the role of a previous HBV infection (defined as the presence of anti-HBcAg antibodies) and the presence of archived resistance-associated mutations (RAMs) to 3TC, based on Stanford algorithm mutations scores (version 9.7). The included population was followed from the moment of the switch to 3TC/DTG (baseline, BL) up to VF and to treatment discontinuation for any cause (TD). For the virological outcome, participants were censored at the last available viral load measurement, TD, or loss to follow-up (absence of at least one HIV-RNA measurement for more than one year). Probability of VF and TD over time were evaluated by Kaplan-Meier estimator. Predictors of VF were subsequently analysed by multivariable Cox regression analysis (including all factors associated with the outcome at univariable analysis at a p-value<0.05). A post-hoc analysis was then conducted to understand if a causal role of potential occult HBV infection on time to VF was present. We analysed differences in demographical and viro-immunological characteristics among PWH with and without anti-HBcAg positive serostatus, by using Chi-square test for categorical variables and Student T-test for independent samples for continuous variables. A multivariable Cox regression model was then fitted to assess the independent role of anti-HBc positivity on VF.

3. Results

A total of 188 patients were included in our study: most were male (141, 75%), Caucasians (174, 92.5%), with a median age of 54 years (IQR 44-61 years). Sexual transmission was the most common route of HIV acquisition, with similar proportions among individuals reporting heterosexual (70, 37.2%) and same-sex sexual contacts (84, 44.7%). Median time since HIV diagnosis was 11 years (IQR 5-17 years), with a median of 9 years since ART initiation (IQR 5-16 years), and 5 years of virological suppression (IQR 3-9). Thirty-five PWH (18.6%) had a history of a previous AIDS defining condition. Complete characteristics of study population are summarized in Table 1.

Table 1. Cohort demographic and immunological and virological data.

Population	N=188 (% or IQR)
Male gender (%)	141 (75.0)
Age, years (IQR)	54 (44-61)
Ethnicity (%)	
Caucasians	174 (92.5)
Africa-Sub-Saharan	4 (2.1)
South America	7 (3.7)
Asians	3 (1.6)
HIV acquisition, risk factor (%)	

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Heterosexual men and women	70 (37.2)
MSM	84 (44.7)
People who inject drugs (PWID)	14 (7.5)
Other/unknown	20 (10.6)
Time since HIV diagnosis, years (IQR)	11 (5-17)
Time since ART initiation, years (IQR)	9 (5-16)
Years of virological suppression (IQR)	5 (3-9)
Previous AIDS event, at least one (%)	35 (18.6)
Nadir CD4+ count (cells/µL), (IQR)	270 (144-385)
Baseline CD4+ count (cells/µL), (IQR)	716 (538-920)
Zenith HIV-RNA (%)	
<100.000 copies/mL	86 (47.2)
100,000-499.999 copies/mL	54 (29.7)
≥500.000 copies/mL	42 (23.1)
Baseline HIV-RNA (%)	
Target not detected	110 (58.5)
Target detected <20 copies/mL	62 (33.0)
20-49 copies/mL	16 (8.5)
Positive HCV-Ab serostatus (%)	19 (10.1)
Number of previous therapeutic lines (IQR)	4 (3-6)

The reason for treatment change was proactive switch in all cases, with 129 (68.6%) patients switching from a 2NRTIs+InSTI regimen. One hundred and twenty-eight PWH (68.1%) had experienced at least one previous VF, while 127 (67.6%) were previously exposed to five or less regimens.

Among participants with at least one genotypic resistance test available before BL (137, 72.9%), 14 (10.1%) had at least one RAM to NRTIs; RAMs to 3TC were detected in 5 (3.6%) participants, with one (0.7%) case of M184V.

Concerning HBV serostatus, most patients (74, 39.4%) were HBV-seronegative, 51 (27.1%) had an isolated anti-HBsAg positivity, 35 (18.6%) showed positivity for both anti-HBsAg and anti-HBcAg. Ten patients (5.3%) showed isolated positivity for anti-HBcAg, 18 (9.6%) had an unknown HBV serostatus.

Sixteen patients (2.87 per 1000 patient-years of follow-up or PYFU) discontinued treatment with 3TC/DTG (Figure 1a). Reasons for TD included: VF (6/16, 37.5%), switch to a long-acting regimen (2/16, 12.5%), drug-related toxicity (5/16, 31.3%), other/unknown cause (3/16, 18.7%). VF was found in 8 (1.45 per 1000 PYFU) patients (Figure 1b).

Estimated probability of time to treatment discontinuation was 1.3% (0.3-5.0) at 12 months of follow-up, 2.8% (1.1-7.4) at 24 months, 7.5% (3.7-14.8) at 36 months, 12.9% (7.0-23.3) at 48 months and 34.5% (18.2-58.9) at 60 months (Figure 1a). Estimated probability of time to virological failure was 0.6% (0.1-0.4) at 12 months, 2.7% (1.0-7.1) at 24 and 36 months, 4.2% (1.7-10.7) at 48 months and 22.3% (7.9-54.3) at 60 months (Figure 1b).

Factors independently associated with VF at multivariable analysis were a baseline HIV-RNA between 20 and 49 copies/mL (versus<20 copies/mL, aHR 9.11, 95 % CI 1.05-79.40; p-value= 0.046), and a higher GSS-score for 3TC (per 10 points more, aHR 1.57, 95 % CI 1.07-2.29; p= 0.023); a borderline significant association was found for anti-HBcAg positive serostatus (versus negative, aHR 8.88 95% CI 0.89-88.45; p= 0.062). Table 2 summarizes explored associations among other potential predictors and the virological outcome (Table 2).

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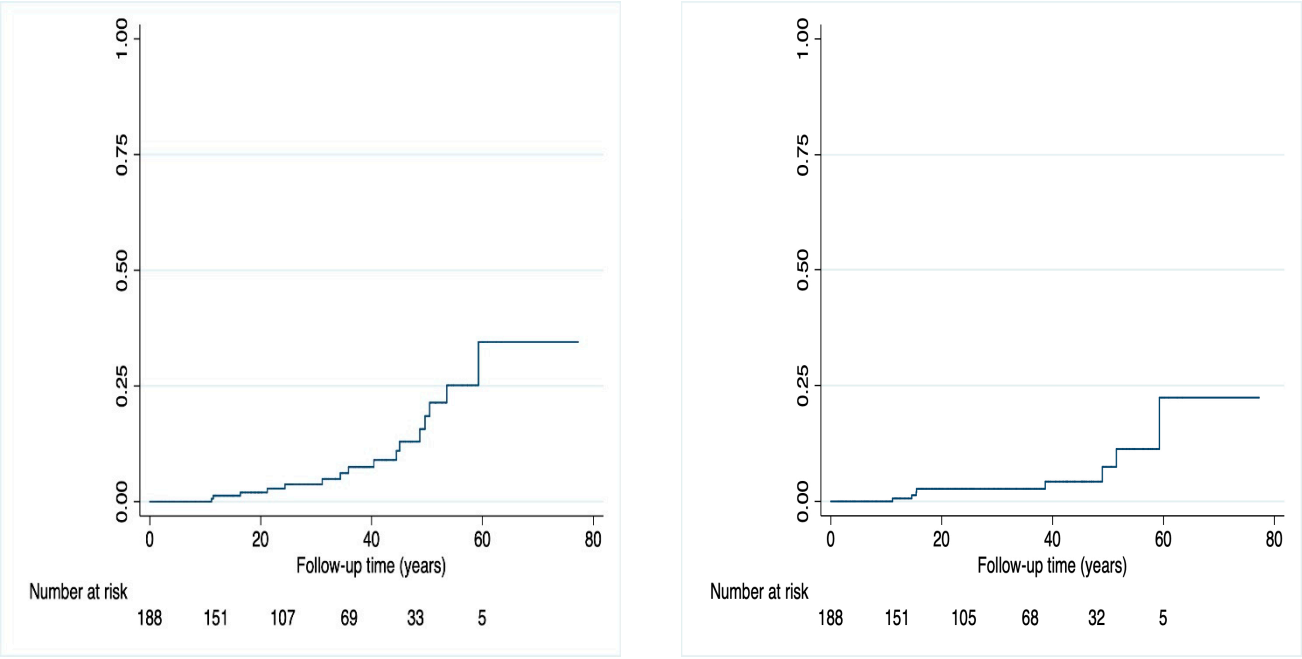

(a) (b)

Figure 1. Estimated probability of time to treatment discontinuation (a) and time to virological failure (b).

Table 2. Cox regression: predictors of time to virological failure.

	HR (95% CI)	p-value	aHR (95% CI)	p-value
Age (per 10 years more)	1.02 (0.54-1.91)	0.953	-	-
Sex (female vs male)	0.44 (0.05-3.60)	0.440	-	-
Nadir CD4 count	0.99 (0.99-1.00)	0.110	-	-
Zenith HIV-RNA	0.99 (0.99-1.00)	0.607	-	-
Years with HIV	1.00 (0.92-1.08)	0.919	-	-
Years of virological suppression	0.88 (0.72-1.07)	0.205	-	-
Baseline HIV-RNA 20-49 copies/ml (versus <20 copies/mL)	5.67 (1.10- 9.39)	**0.039**	9.11 (1.05-79.40)	**0.046**
GSS*-3TC (per 10 points more)**	1.74 (1.23-2.48)	**0.002**	1.57 (1.07-2.29)	**0.023**
Pre-switch tenofovir exposure	1.87 (0.44-7.84)	0.395	-	-
Anti-HBcAg + (vs negative)	5.76 (1.26-26.24)	**0.024**	8.88 (0.89-88.45)	0.062
HBV serology:				
- AntiHBcAg-/AntiHBsAg-	-	-	-	-
- AntiHBcAg-/AntiHBsAg+	1.43 (0.41-5.02)	0.574	-	-
- AntiHBcAg+/AntiHBsAg+	1.71 (0.41-7.23)	0.466	-	-
- AntiHBcAg+/Anti HBsAg-	2.69 (0.31-3.30)	0.368	-	-

* GSS: genotypic susceptibility score.

Among PWH with and without anti-HBcAg positive serostatus, gender and age were significantly different, with a higher proportion of men with older age in the anti-HBcAg-positive group. Interestingly, fewer PWH in the anti-HBcAg-positive group switched from a tenofovir-containing strategy (see Table 3).

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Table 3. Population characteristics according to anti-HBcAg serostatus and risk of virological failure.

	Anti-HBcAg + n=45 (%)	Anti-HBcAg - n=135 (%)	p-value
Sex (male)	41 (91.1)	95 (70.3)	**0.005**
Age (years, IQR)	58 (55-61)	52 (50-54)	**0.002**
Risk factor			
Hetero	11 (24.4)	55 (40.7)	
MSM	23 (28.1)	59 (43.7)	0.120
IDU	3 (6.6)	10 (7.4)	
Other/Unknown	8 (1.7)	11 (8.1)	
Years with HIV (IQR)	14.43 (11.64-17.23)	11.74 (10.31-13.18)	0.072
Years of suppression (IQR)	7.27 (5.37-9.18)	5.85 (5.09-6.62)	0.101
CD4 baseline (IQR)	644 (493-857)	734 (548-947)	0.109
HIV-RNA detectable (20-49 copies/mL)	4 (8.8)	11 (8.1)	0.987
Tenofovir exposure pre-switch	15 (33.3)	72 (53.3)	**0.020**
Previous virological failure	13 (28.8)	32 (23.7)	0.651
3TC* resistance associated mutations	2 (4.4)	3 (2.2)	0.695

After stratifying anti-HBcAg serostatus for prior tenofovir exposure we found a 15 times fold higher risk of VF for PWH with anti-HBcAg positivity and previous exposure to tenofovir (versus negative anti-HBcAg and no prior tenofovir use, aHR 15.06, 95% CI 1.40-161.38; p-value= 0.025), whereas the effect of anti-HBcAg serostatus was markedly reduced in those not switching from a tenofovir-based therapy and did not reach statistical significance (Table 4).

Table 4. Cox regression for risk of virological failure per anti-HBcAg serostatus and previous tenofovir exposure.

	aHR (95% CI)	p-value
Previous tenofovir use and occult infection:		
- No prior tenofovir plus anti-HBcAg–	Reference	Reference
- Prior tenofovir plus anti-HBcAg –	1.51 (0.13-16.92)	0.738
- No prior tenofovir plus anti-HBcAg+	2.62 (0.14-47.41)	0.513
- Prior tenofovir plus anti-HBcAg+	**15.06 (1.40-161.38)**	**0.025**
Age (per 10 years more)	0.93 (0.43-2.04)	0.859
Sex (female vs. male)	NA	NA

4. Discussion

Dual ART regimen with 3TC/DTG was highly effective in our cohort of virologically suppressed PWH undergoing antiretroviral therapy optimization. The most recent European guidelines underline the possibility of switching to 3TC/DTG in the setting of previous VF and/or in the presence of M184I/V, whereas, concerning HBV serological status, a switch should be considered in the presence of anti-HBs antibodies (even if no absolute contraindications have been provided concerning isolated anti-HBcAg positivity). [1,2].

In our study, anti-HBcAg was associated with an almost 9-time higher risk of VF, and 15-times higher for those who discontinued tenofovir.

To date, no evidence has emerged of an increased risk of VF with 3TC/DTG in the setting of prior HBV infection. However, a large study from the Italian ICONA cohort by Malagnino et al. did find an excess of risk of VF in case of isolated anti-HBcAg positivity, irrespectively of ART regimen, even

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if this risk was lower compared with active HBV infection [4]. Also, another work by Malagnino et al. reported significantly fewer anti-HBcAg-positive PWH reaching the target not detected-level of HIV-RNA, compared with anti-HBcAg-negative subjects, in a cohort of people switching to 3TC/DTG; moreover, anti-HBcAg positivity was the only factor associated with an increased risk of suboptimal HIV suppression [16]. Conversely, a similar study conducted in China on 601 PWH switching to 3TC/DTG showed no differences in the proportion of PWH with non-detectable viremia after 24 months from switch [17]. Finally, in another Italian cohort of 606 virologically suppressed PWH switching to 3TC/DTG, no significant differences by HBV serostatus were observed regarding the risk of virological failure or viral blips; however, the effect of HBV serology was not adjusted for potential confounders [18].

Another unresolved issue is represented by the absence of a confirmed biological explanation for a reduction of antiretroviral therapy efficacy in the context of prior HBV exposure. Recently, replication of cryptic serum HBV-DNA was demonstrated in a cohort of anti-HBc-positive/HBsAg-negative PWH despite present tenofovir exposure [19]. However, after switching to a tenofovir-sparing regimen (mostly based on 3TC), the rate of PWH experiencing HBV-DNA>10 IU/mL increased from 12.9% at T1 to 42.6% at T2 and was predicted by a lower nadir CD4 count and the presence of cryptic HBV-DNA at baseline. Even if failure in HIV control was not specifically reported during follow-up, this study seems to support a previously proposed hypothesis [16,20] concerning the synergistic viral interplay of HIV-HBV coinfection, with the reduction of selective antiviral drug pressure or development of HBV-resistance to 3TC, causing HBV to rebound and/or replicate at low levels which, in turn, could activate HIV transcription through HBx activity [20].

In the present study, a higher risk of VF was also predicted by the presence of RAMs to 3TC at previous genotypic resistance tests. This topic has been object of extensive debate in last few years, with no definite proof of a causal effect of the most important mutation to 3TC, M184I/V, on virological outcomes. In the pilot ART-PRO clinical trial, no signal of increased VF risk at 144 week was found in a cohort of PWH with past M184I/V, but with the demonstrated absence of the mutation at screening GRT performed on HIV-DNA [21]. More recently, the SOLAR-3D clinical trial, enrolling individuals with and without a history of M184I/V (some of whom with mutation also detected at baseline genotypic test on HIV-DNA), confirmed the lack of differences in the rate of virological suppression and viral rebound at 144 weeks [22]. In contrast with these trials, one retrospective study underlined the effect of M184I/V in increasing the risk of viral rebound, especially when the mutation was present in association with at least one TAM, independently from the time of virological suppression before switch [23]. Moreover, an emulated trial from the Italian ARCA cohort showed an increased risk of failing with the dual regimen if the switch occurred within the first 6 months from virological suppression and in the presence of historical RAMs (both TAMs and isolated M184I/V), with also a non-statistically significant superior efficacy of triple therapy being reported in this setting [24]. Despite the discrepancy in these results, that could be partly attributed to the different study populations and methods, it is not possible to completely exclude the role of previously found-RAMs on the efficacy of the two-drug regimen, and caution is still advisable when considering this strategy for people with a previous history of failure, even if the overall risk of failure, especially with resistance development, remains very low [25].

Our study has clearly some limitations, primarily due to the low incidence of the virological outcome and the possibility of overfitted statistical models. Another limitation lies in the retrospective design of the study and the impossibility of capturing important data, such as patients' adherence or, importantly, the determination of HBV-DNA at baseline and at failure (that could have supported the presence of occult HBV infection as the cause of VF). Finally, given the monocentric design, results lack generalizability.

Despite these limitations, this study partly confirms results from other cohorts about the role of RAMs on VF and adds further evidence of a potential concern on the effect of prior HBV infection when switching to a tenofovir-sparing regimen. Considering that most of next-generation treatment

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strategies won't have antiviral activity on HBV infection, further evidence on this topic is now mandatory.

5. Conclusions

We found that 3TC/DTG was safe and effective coherently with the available literature. In the few cases in which VF was encountered, predictors for VF were a detectable viremia at baseline, archived RAMs to 3TC, and a positive anti-HBcAg serostatus; the latter was particularly relevant in case of pre-switch exposure to tenofovir. Despite the limitations of our study, we think that reasoning on specific viro-immunological characteristics (e.g., time of viral suppression, persistence of RAMs over time, detection of occult HBV infection) is still fundamental when considering optimization to 3TC/DTG.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Pisa University Hospital (protocol AHCS, version 1.0, approval date 4th of July, 2024).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: A.B. participated in Advisory boards for ViiV Healthcare, Gilead Sciences and Merck Sharp and Dhome. M.F. received unconditional grants from Gilead and speaker honoraria from Pfizer, Menarini, Gilead, GSK, and TermoFisher. The remaining authors declare no conflicts of interest. .

Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
3TC	Lamivudine
3TC/DTG	Lamivudine/Dolutegravir
PWH	People Living with HIV
ART	Antiretroviral Therapy
VF	Virological Failure
RAMs	Resistance Associated Mutations
OBI	Occult HBV Infection
TD	Treatment Discontinuation
PYFU	Patient Year of Follow-Up
HR	Hazard Ratio
CI	Confidence Interval
GSS	Genotypic Susceptibility Score
PrEP	Pre-Exposure Prophylaxis
MSM	Males who have Sex with Males
HCV	Hepatitis C Virus
IDU	Intravenous Drug Users
NRTI	Nucleoside Reverse Transcriptase Inhibitor
INSTI	Integrase Strand Transfer Inhibitor.

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