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Predictors and Outcomes of HIV-Infected Antiretroviral-Naïve Patients with Discordant Responses to Combination Antiretroviral Treatment in Asian and Australian Populations: Results from APHOD

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To the Editors

Some patients experience a 'discordant response' after the initiation of combination antiretroviral treatment (cART), whereby the HIV-1 RNA plasma level is below the limit of detection but the CD4 T-cell count response is blunted.[1–6] Other patients exhibit a different pattern of discordant response, characterized by a sustained CD4 T-cell count response, despite persistent viremia.[1–6] Although there have been studies on discordant responses,[1–8] there is still limited knowledge about the clinical significance of such a response. Furthermore, there are no published data on discordant responses within the Asia-Pacific region. The objective of this analysis was to evaluate predictors of discordant response and their outcomes among HIV-Infected antiretroviral-naïve patients on cART from Asian and Australian populations.

We analysed the Asia-Pacific HIV Observational Database (APHOD), a prospective, observational cohort study of adults with HIV from 26 sites across Australia (the Australian HIV Observational Database [AHOD])[9] and 18 sites from the Asia-Pacific regions (the TREAT Asia HIV Observational Database [TAHOD]).[10] The structure of these databases and standardized mechanisms for data collection and follow-up, have been previously described.[9–10] All antiretroviral-naïve participants who initiated cART between 1996 and 2008, aged 16 years or older at treatment initiation, had a known date of therapy initiation, and had at least 1 measurement (CD4 T-cell count and HIV viral load) at 24 months of therapy (within a window of +/−3 months) were eligible for inclusion in analyses. Virologic response (VR) was defined as HIV viral load <500 copies/mL at 6 months, 12 months, and 24 months after initiation of cART. Immunologic response (IR) was defined as a rise in CD4 T-cell count of at least 50 cells/μL or a CD4 T-cell count more than 350 cells/μL at 6

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months after initiation of cART. IR was also defined as a rise in CD4 T-cell count of at least 100 cells/μL or a CD4 T-cell count more than 350 cells/μL at 12 months and 24 months after initiation of cART. The exposures of interest were 6, 12, and 24 month responses to therapy, categorized according to VR and IR, considered jointly as complete response (VR+/IR+), virologic only response (VR+/IR−), immunologic only response (VR−/IR+), and complete failure (VR−/IR−). To evaluate predictors of poor immunologic recovery in the context of effective virologic suppression, we performed logistic regression analyses including subjects with virologic suppression at 6, 12, and 24 months after cART initiation. We investigated outcomes following concordant or discordant responses using survival analyses methods. The primary endpoint to evaluate outcomes was all cause mortality or new AIDS-defining illness documented after the 24-month time point. The survivor function for AIDS diagnosis or death of the discordant responses at 24 month was compared using Kaplan-Meier curve. Time was calculated from the 24-month time point following treatment initiation and ended at the appropriate endpoint (new AIDS or death), or the last follow-up visit. Discordant data at 6 or 12 months after cART initiation were included in the final multivariate model separately. The analyses were performed using SAS (version 9.1, SAS Institute Inc., Cary, North Carolina, USA) and STATA (version 10.1, StataCorp, College Station, Texas, USA).

A total 2157 participants were eligible for this analysis: 1036 from AHOD and 1121 from TAHOD (Table S1). At 6 months, 68% patients had complete response; 15% had virologic-only response; 12% had immunologic only response; and 5% showed complete failure (Table S2). At 12 months, 63% patients had complete response; 19% had virologic-only response; 12% had immunologic only response; and 6% showed complete failure. At 24 months, 70% patients had complete response; 13% had virologic-only response; 11% had immunologic only response; and 6% showed complete failure.

In patients with a VR, factors associated with a discordant IR at 6, 12, and 24 months on multivariate analyses were consistent at all three time points (Table S3), although the magnitude of effects and statistical significance did vary. Female patients were less likely than males to have a poor IR. Compared to patients reporting homosexual contact, patients reporting injecting drug use and heterosexual contact as their mode of HIV acquisition were more likely to have a poor IR. Prior AIDS diagnosis at cART initiation was associated with a poor IRat 12 months after cART initiation. There was a borderline significant association of hepatitis C coinfection with poor IR at6 months, but this association was not observed at 12 and 24 months. Higher CD4 T-cell count and lower viral load (<50,000 copies/mL) at cART initiation were associated with lower risk of poor IR at all three time points. Finally, initial cART containing didanosine (ddI) was associated with a higher risk of poor IR, most notable 12 months after cART initiation.

We evaluated the prognostic significance of discordant responses on disease progression (newly developed AIDS or death) (Table 1). There were 150 newly developed AIDS or death events reported during 10876person years of follow-up (an incidence of 1.38per 100 person years, 95% CI 1.18–1.62). In multivariate model, hepatitis C coinfection was associated with a higher risk of disease progression. Patients having higher baseline CD4 T-cell counts, especially greater than 200 cells/μL, were at significantly lower risk of disease progression. Compared to patients with complete response (VR+/IR+), patients with a virologic only response (VR+/IR−) at 6, 12, and 24 months had similar risk of disease progression, however patients with an immunologic only response (VR−/IR+) or complete failure (VR−/IR−) had significantly increased risk of disease progression. The Kaplan-Meier curve summarizing time to death or new AIDS diagnosis indicated that disease progression differed significantly according to immunologic and virologic responses at 24 months after initiating cART (log rank test, $P<0.001$)(Fig. S1). The prognosis was best for

the VR+/IR+ and VR+/IR− group, worst for the VR−/IR− group, and intermediate for the VR−IR+ group. However, the difference between the VR+/IR+ group and the VR+/IR− group was not statistically significant (*P*=0.502). When included in the final multivariate model, immunologic only responses at 12 and 24 months had significantly higher risk for disease progression than complete response. However, those with virologic only responses at 6, 12 and 24 months had a similarly good outcomes to those with complete responses.

The data suggest that in the first two years VR is more important than IR in terms of survival and HIV disease progression. However, further research is warranted to establish the importance of IR beyond the initial 2-year treatment period, since lower CD4 counts are associated with higher risk of AIDS as well as serious non-AIDS events.[11] A limitation of our study is the absence of some important variables such as adherence and concomitant medications, particularly cytotoxic drugs. In addition, the small number of patients with treatment response, either VR+/IR−, VR−/IR+ or VR−/IR−, may have limited statistical power. Collaboration with other cohorts is warranted to increase the number and the power. Further studies are needed to elucidate the prognostic significance of virologic only and immunologic only responses with clear definitions, and clinical trials are required to identify the most appropriate intervention in patients who are at elevated risk of disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cox proportional hazards analysis of all-cause mortality or newly-developed AIDS for 2157 HIV-infected individuals

Variable	Unadjusted HR	95 % CI	P value	Adjusted HR	95 % CI	P value
Age (year) at cART initiation						
<=25	1.00					
26–35	0.76	(0.39, 1.51)	0.438			
36–45	0.79	(0.40, 1.57)	0.497			
46+	0.93	(0.46, 1.89)	0.844			
Gender						
Male	1.00					
Female	0.93	(0.55, 1.56)	0.770			
Reported route of infection						
Homosexual contact	1.00			1.00		
Injecting drug use	1.90	(1.05, 3.42)	0.033	1.01	(0.52, 1.97)	0.974
Heterosexual contact	0.99	(0.62, 1.59)	0.978	0.90	(0.55, 1.47)	0.668
Prior AIDS diagnosis at cART initiation						
No	1.00					
Yes	1.13	(0.76, 1.69)	0.539			
Hepatitis B coinfection						
No	1.00			1.00		
Yes	1.68	(0.98, 2.90)	0.061	1.54	(0.89, 2.67)	0.124
Hepatitis C coinfection						
No	1.00			1.00		
Yes	1.93	(1.23, 3.04)	0.004	1.93	(1.21, 3.07)	0.005
CD4 T-cell count (cells/μL) at cART initiation						
<=50	1.00			1.00		
51–100	0.77	(0.39, 1.53)	0.458	0.68	(0.34, 1.35)	0.269
101–200	0.72	(0.43, 1.21)	0.212	0.61	(0.36, 1.03)	0.065
201–300	0.39	(0.21, 0.74)	0.004	0.36	(0.19, 0.69)	0.002
301 or more	0.57	(0.35, 0.93)	0.025	0.59	(0.36, 0.98)	0.040
HIV viral load (copies/ml) at cART initiation						
50001+	1.00			1.00		

Variable	Unadjusted HR	95 % CI	P value	Adjusted HR	95 % CI	P value
<500	1.08	(0.68, 1.71)	0.739	1.33	(0.83, 2.14)	0.236
501–10000	0.99	(0.51, 1.93)	0.975	1.15	(0.58, 2.28)	0.699
10001–50000	0.16	(0.02, 1.16)	0.070	0.17	(0.02, 1.26)	0.084
Discordant data at 6 months after cART initiation						
VR+IR+	1.00			1.00		
VR+IR−	1.07	(0.58, 1.97)	0.838	0.90	(0.47, 1.72)	0.743
VR−IR+	2.21	(1.39, 3.50)	0.001	1.60	(0.98, 2.59)	0.059
VR−IR−	2.08	(1.06, 4.08)	0.033	0.92	(0.43, 1.96)	0.835
Discordant data at 12 months after cART initiation						
VR+IR+	1.00			1.00		
VR+IR−	0.98	(0.55, 1.76)	0.955	0.88	(0.47, 1.67)	0.705
VR−IR+	2.38	(1.49, 3.79)	<0.001	1.73	(1.02, 2.92)	0.041
VR−IR−	3.95	(2.41, 6.47)	<0.001	2.04	(1.09, 3.81)	0.026
Discordant data at 24 months after cART initiation						
VR+IR+	1.00			1.00		
VR+IR−	1.16	(0.67, 2.00)	0.602	1.36	(0.77, 2.40)	0.287
VR−IR+	1.81	(1.15, 2.84)	0.010	1.71	(1.08, 2.69)	0.021
VR−IR−	4.47	(2.89, 6.91)	<0.001	4.94	(3.17, 7.72)	<0.001

Discordant information at 6 or 12 months after cART initiation was added separately into the multivariate model. cART; combination antiretroviral treatment, VR; virologic response, IR; immunologic response