


# Nocturnal dipping of heart rate and blood pressure in people with HIV in Tanzania

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## Abstract

People with HIV (PWH) have a >2-fold greater risk for development of cardiovascular disease (CVD), which may be associated with abnormalities in 24-h ambulatory blood pressure measurement (ABPM) profile. We conducted a nested case-control study of ABPM in 137 PWH and HIV-uninfected controls with normal and high clinic blood pressure (BP) in Tanzania. Nocturnal non-dipping of heart rate (HR) was significantly more common among PWH than HIV-uninfected controls ( $p = .01$ ). Nocturnal non-dipping of BP was significantly more common in PWH with normal clinic BP ( $p = .048$ ). Clinical correlates of nocturnal non-dipping were similar in PWH and HIV-uninfected adults and included higher BMI, higher CD4<sup>+</sup> cell count, and high C-reactive protein for HR and markers of renal disease for BP. In conclusion, nocturnal non-dipping of both BP and HR was more common in PWH but further research is needed to determine causes and consequences of this difference.

## 1 | INTRODUCTION

Ambulatory blood pressure monitoring (ABPM)—the measurement of blood pressure (BP) over a 24-h period—is the reference standard for BP measurement.<sup>1</sup> ABPM results predict cardiovascular disease (CVD) events and mortality more accurately than clinic BP measurements.<sup>2</sup> Additionally, ABPM allows for the identification of high-risk phenotypes—including nocturnal non-dipping of BP and heart rate (HR)—which cannot be diagnosed in the clinic.

People with HIV (PWH) have a twofold to fourfold higher incidence of CVD.<sup>3,4</sup> This increased risk may be partly attributable to abnormalities in nocturnal BP and HR.<sup>5</sup> We do not yet know whether these ABPM abnormalities observed in PWH differ by clinic BP status.

Therefore, we conducted a nested case-control study comparing ABPM in PWH with normal and high clinic BP and HIV-uninfected controls in Tanzania. Objectives of this research were as follows: 1) to compare nocturnal non-dipping of BP and HR between PWH and HIV-uninfected controls and 2) to determine

Cody Nolan and Karl Reis have contributed equally to the work.

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correlates of nocturnal non-dipping of BP and HR in PWH and HIV-uninfected controls.

## 2 | METHODS

### 2.1 | Study cohort

This nested case-control study was conducted within a well-described prospective cohort<sup>6</sup> of PWH attending an outpatient HIV clinic in Tanzania and HIV-uninfected controls.

### 2.2 | Study population

Cohort inclusion criteria include age 18-65 years, Tanzanian citizenship, and residing in Mwanza City. Exclusion criteria for both groups include previous history of CVD and a medical condition with a prognosis of <12 months.

### 2.3 | Study location

All study activities were performed in the outpatient HIV clinic at Bugando Medical Centre, in Mwanza, Tanzania.

### 2.4 | Study procedures

Study procedures have been described in detail previously.<sup>6</sup> At each study visit, a standardized questionnaire and physical examination were administered. Automated BP was measured using an OMRON HBP-1300 (OMRON Healthcare) professional BP monitor. High clinic BP was defined as BP measurements ( $\geq 140/90$  mmHg) on at least two consecutive visits according to the International Society of Hypertension (ISH) threshold.<sup>7</sup>

### 2.5 | Ambulatory blood pressure monitoring study design

From February 2018 to June 2018, we performed ABPM on 50 consecutive cohort participants attending scheduled research clinic appointments with normal clinic BP. We also performed ABPM on all participants with high clinic BP.

### 2.6 | Ambulatory blood pressure measurement

Ambulatory blood pressure monitoring was performed using the validated SunTech Medical® Oscar 2 machine, programmed via the AccuWin Pro 4 software to measure BP for 24 h at an interval of 15 min. Initial readings were confirmed in-clinic. Participants

were instructed to return to the clinic after 24 h. The following day self-reported sleep and wake times were recorded. All participants identified as hypertensive were referred to a physician and offered free hypertension treatment according to the Tanzanian guidelines.<sup>8,9</sup> All ABPM met European Society of Hypertension (ESH) quality control guidelines for ABPM, which require >20 daytime and >7 nighttime measurements, and  $\geq 70\%$  valid measurements of expected measurements. Nocturnal non-dipping of HR/BP was defined as an asleep HR/BP reduction of  $\geq 10\%$  of awake values.<sup>10</sup>

### 2.7 | Laboratory procedures

CD4<sup>+</sup> T-cell count was measured using an automated BD FACS Calibur Machine (BD Biosciences) for PWH. Serum creatinine level was measured using the A25 Analyzer (Biosystems), calibrated by the creatinine Jaffé 2 method. An estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation.<sup>11</sup> Urine albumin and creatinine were measured with the Siemens DCA Vantage Analyzer (Siemens Healthcare). High-sensitivity serum C-reactive protein (hsCRP) concentration was measured using R&D Systems Quantikine ELISA (R&D Systems). hsCRP measurements were classified according to cardiovascular risk,<sup>12</sup> with hsCRP >3 mg/L representing high risk and hsCRP  $\leq 3$  mg/L representing low/intermediate risk.

### 2.8 | Statistical methods

Data were double entered into OpenClinica (OpenClinica LLC). Baseline participant characteristics were summarized using median and interquartile range for continuous variables and frequency and percent for categorical variables. For categorical variables, chi-squared tests or Fisher's exact tests, as appropriate, were performed to evaluate the association between HIV status and BP/HR dipping status. Multivariate logistic regression analyses adjusted for clinic systolic blood pressure (SBP) were used to evaluate factors associated with nocturnal non-dipping of BP/HR. All analysis was conducted using Stata version 15.1 (STATACorp LLC).

### 2.9 | Ethics

The study was carried out in accordance with Good Clinical Practice and the Declaration of Helsinki. The study and consent forms were approved by the Weill Cornell Medicine (1506016328), the Tanzanian National Institute of Medical Research (NIMR/HQ/R.8c/Vol.1/1399), and Bugando Medical Centre (CREC/074/2015). All participants provided written informed consent.

### 3 | RESULTS

#### 3.1 | Study population and characteristics

The baseline characteristics of all study participants are displayed in Table S1. Of the 137 participants selected, 50 had normal clinic BP (25 PWH and 25 HIV-uninfected) and 87 had high clinic BP (31 PWH and 56 HIV-uninfected). None of the participants had started anti-hypertensive medication at the time of ABPM measurement. All of the PWH were on ART. Mean duration of ART use was 1.46 years and ranged from 0 to 3.15 years. PWH and HIV-uninfected controls were similar in age, sex distribution, and BMI (Table S1). Analysis of the associations between HIV infection and ABPM results are in Table S2.

#### 3.2 | Nocturnal non-dipping of BP/HR in all participants

Overall, PWH had a higher prevalence of nocturnal non-dipping of HR (39.3% [22/56] in PWH vs. 19.8% [16/81] in HIV-uninfected controls,  $p = .01$ ) than HIV-uninfected controls. Nocturnal non-dipping

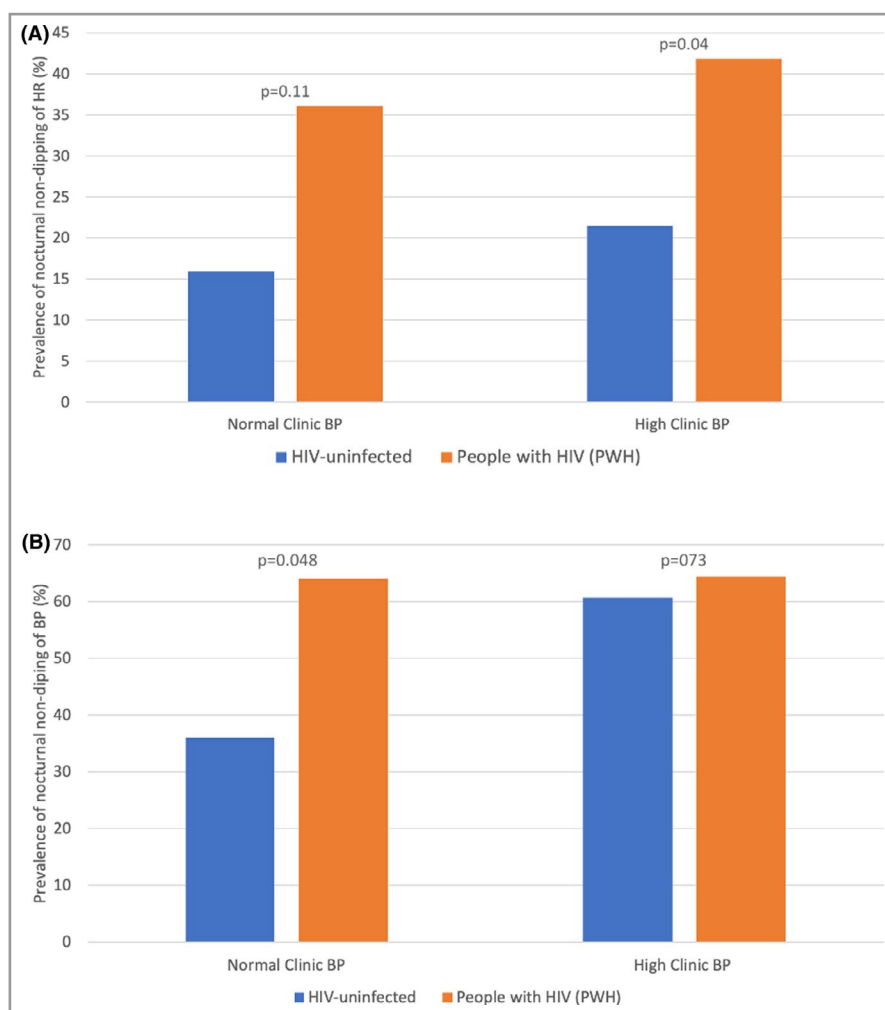
of BP was more common in PWH but this did not reach statistical significance (64.2% [36/56] in PWH vs. 53.1% [43/81] in HIV-uninfected controls,  $p = .19$ ).

#### 3.3 | Nocturnal non-dipping of BP/HR in participants with normal versus high clinic BP

Prevalence of nocturnal non-dipping of HR/BP stratified by HIV status and clinic BP is displayed in Figure 1 and Table S3. Among participants with normal clinic BP, PWH had a higher prevalence of nocturnal non-dipping of BP (64.0% [16/25] in PWH vs. 36.0% (9/25) in HIV-uninfected controls,  $p = .048$ ). Among participants with high clinic BP, PWH had a higher prevalence of nocturnal non-dipping of HR (41.9% [13/31] in PWH vs. 21.4% [12/56] in HIV-uninfected controls,  $p = .043$ ) than HIV-uninfected controls.

#### 3.4 | Correlates of non-dipping

Factors associated with nocturnal non-dipping of HR and BP independent of clinic SBP were similar in PWH and HIV-uninfected



**FIGURE 1** Nocturnal non-dipping of heart rate (HR) and blood pressure (BP) among people with HIV (PWH) and HIV-uninfected control participants stratified by clinic BP. Panel A: Prevalence of nocturnal non-dipping of HR by HIV status. Panel B: Prevalence of nocturnal non-dipping of BP by HIV status

**TABLE 1** Correlates of nocturnal non-dipping of blood pressure (BP)/heart rate (HR) in people with HIV (PWH), HIV-uninfected controls, and all participants in multivariate logistic regression models adjusted for clinic systolic blood pressure

	All participants (n = 137)	PWH (n = 56)	HIV-uninfected (n = 81)
Nocturnal non-dipping of HR			
BMI	1.10 [1.02-1.18]*	1.08 [0.97-1.20]	1.14 [1.01-1.28]*
High hsCRP	2.32 [1.06-5.11]*	1.86 [0.60-5.70]	1.88 [0.56-6.34]
CD4 <sup>+</sup> T-cell count*	1.08 [0.97-1.21]	1.19 [1.00-1.42]*	1.14 [0.95-1.38]
Nocturnal non-dipping of BP			
eGFR < 60 ml/min/1.73m <sup>2</sup>	4.48 [1.18-16.99]*	- <sup>a</sup>	3.45 [0.83-14.3]
ACR ≥ 30 mg/g	3.96 [1.05-14.86]*	6.84 [0.71-65.75]	2.36 [0.43-13.13]

<sup>a</sup>All PWH with eGFR ≥ 60 ml/min/1.73m<sup>2</sup> had nocturnal non-dipping of BP.

\**p* < .05.

adults and are displayed in Table 1. Nocturnal non-dipping of HR was associated with higher BMI (aOR 1.10, 95% CI 1.02-1.18, *p* = .012), elevated hsCRP (aOR 2.32, 95% CI 1.05-5.11, *p* = .036), and CD4<sup>+</sup> T-cell count per 100 cells/mm<sup>3</sup> among PWH (aOR 1.19, 95% 1.00-1.42, *p* = .048). Nocturnal non-dipping of BP was associated with eGFR <60 ml/min/1.73m<sup>2</sup> (aOR 4.48, 95% CI 1.18-16.99, *p* = .027) and ACR ≥30 mg/g (aOR 3.96, 95% CI 1.05-14.86, *p* = .042).

## 4 | DISCUSSION

In this study of ABPM in Tanzania, we report that PWH have a higher prevalence of nocturnal non-dipping of both HR and BP than HIV-uninfected participants. Overall, PWH were twice as likely (40% vs. 20%) to have nocturnal non-dipping of HR. In addition, PWH with normal clinic BP were twice as likely to have nocturnal non-dipping of BP (64% vs. 36%). Correlates of nocturnal non-dipping were similar in PWH and HIV-uninfected adults: HR non-dipping was associated with higher BMI, higher CD4<sup>+</sup> cell count, and high hsCRP, and BP non-dipping was associated with both albuminuria and reduced eGFR.

Nocturnal non-dipping of HR was twice as common in PWH as in HIV-uninfected controls, regardless of BP status (40% vs. 20%). To the best of our knowledge, we are the first to report this higher rate of nocturnal non-dipping of HR in PWH. Emerging data indicate that nocturnal non-dipping of HR may independently predict CVD events and mortality in the general population.<sup>13</sup> Nocturnal non-dipping of HR was independently associated with higher hsCRP, indicating that non-dipping of HR in PWH could be related to chronic vascular inflammation. Nocturnal non-dipping of HR might partly explain the known association between elevated CRP and CVD and could provide a target for intervention.

Two-thirds of PWH and half of HIV-uninfected participants exhibited nocturnal non-dipping of BP. This difference was particularly pronounced among participants with normal clinic BP, where two-thirds of PWH and just one-third of HIV-uninfected controls had nocturnal non-dipping of BP. In the general population, this "normotensive non-dipper" phenotype has been

associated with higher rates of CVD events independent of daytime BP, but this phenotype not been studied in PWH.<sup>14</sup> Previous studies of nocturnal non-dipping of BP in PWH have consistently shown higher rates of nocturnal non-dipping of BP compared with HIV-uninfected adults, but have not investigated whether this difference varied by clinic BP status.<sup>5</sup> Normotensive nocturnal non-dipping of BP deserves further investigation as possible new targets for CVD prevention in PWH.

Our study has limitations, including the small sample size and cross-sectional study design. In addition, HIV viral load was not performed at our clinic at the time of the study due to a national stockout of reagent. Lastly, due to the manual labor required daily in Tanzania, many participants had 1-2 h per day when they did not meet the final ESH quality control criteria of ≥2 valid measurements per daytime hour and ≥1 valid measurement per nighttime hour. However, studies indicate that ABPM with as few as eight daytime readings and four nighttime readings likely still retain diagnostic and predictive accuracy.<sup>15</sup>

In conclusion, PWH had a higher prevalence of nocturnal non-dipping of BP and HR. Future research should determine the causes and consequences of nocturnal non-dipping of BP and HR in PWH to determine if non-dipping could be a novel target for intervention to prevent CVD in PWH.

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## CONFLICT OF INTEREST

The authors report no conflicts of interest.

## AUTHOR CONTRIBUTIONS

CN contributed to study conception, design, data collection, and revised manuscript for important intellectual content. KR contributed to data collection, data analysis, data interpretation, manuscript preparation, and revised manuscript for important intellectual content. SF contributed to data collection, data analysis, and revised manuscript for important intellectual content. AE contributed to

data analysis, data interpretation, and revised manuscript for important intellectual content. CE contributed to data analysis, data interpretation, manuscript preparation, and revised manuscript for important intellectual content. JK contributed to study conception, study design, data collection, manuscript preparation, and revised manuscript for important intellectual content. CM contributed to study conception, study design, manuscript preparation, and revised manuscript for important intellectual content. ML contributed to study design, data analysis, data interpretation, manuscript preparation, and revised manuscript for important intellectual content. SK contributed to study conception, study design, data interpretation, manuscript preparation, and revised manuscript for important intellectual content. RP contributed to study conception, study design, data collection, data analysis, data interpretation, manuscript preparation, and revised manuscript for important intellectual content.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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