



BIKTARVY®

bictegravir 50mg/emtricitabine 200mg/
tenofovir alafenamide 25mg tablets



Building confidence together

UK data from a long-running HIV real time sample study* shows that, from January to December 2021, **Biktarvy was the number one naïve product prescribed by participating doctors.**^{1*}

The same study shows that, from January to December 2021, for participating doctors, Biktarvy was one of the top preferred switch options, and that 72% of patients prescribed Biktarvy were switched over from a non-TAF regimen.^{2†}

Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.^{3,4}

For healthcare professionals only

This study is a syndicated report, with no influence on design from Gilead, nor is it using a Gilead (or any other manufacturer) target list to recruit physicians.¹²

* This includes 1,168 patients naïve to ART, across 12 months (January-December 2021).¹ 47 doctors reporting on 1,168 initiating patients in the UK.¹ Use of Biktarvy as a regimen for all initiating patients from January to December 2021 was 25%.¹

† This study includes 1,169 existing ART patients who switched during these 12 months.² 47 doctors reporting on 1,169 HIV patients switching to a new regimen at the time of visit in the UK.² Use of Biktarvy as a regimen among all switching patients from January to December 2021 was 17%.²

References:

1. Data on file (naïve), Gilead Sciences. January 2022.
2. Data on file (switch), Gilead Sciences. January 2022.
3. Biktarvy Summary of Product Characteristics (England, Scotland and Wales).
4. Biktarvy Summary of Product Characteristics (Ireland and Northern Ireland).

This is a stock image and not a person living with HIV

ART, Anti-retroviral therapy; HIV, Human immunodeficiency virus;
TAF, tenofovir alafenamide.


UK-BVY-0317 May 2022

[Click here](#) for Biktarvy prescribing information

Adverse events should be reported. For Great Britain and Northern Ireland, reporting forms and information can be found at www.mhra.gov.uk/yellowcard/ or via the Yellow Car app (download from the Apple App Store or Google Play Store). Adverse events should be reported to Gilead (safety_FC@gilead.com) or +44 (0) 1223 897500.

ORIGINAL ARTICLE

Estimating the risk of mortality attributable to recent late HIV diagnosis following admission to the intensive care unit: A single-centre observational cohort study

Nicholas Bakewell^{1,2} | Tanmay Kanitkar^{3,4} | Oshani Dissanayake⁴ |
Maggie Symonds⁴ | Stephanie Rimmer³ | Amit Adlakha³ | Marc C. Lipman^{4,5,6} |
Sanjay Bhagani⁴ | Banwari Agarwal³ | Robert F. Miller^{4,7} | Caroline A. Sabin^{1,2} 

¹Institute for Global Health, University College London, London, UK

²National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Blood Borne and Sexually Transmitted Infections, University College London, London, UK

³Intensive Care Unit, Royal Free Hospital, Royal Free London NHS Foundation Trust, London, UK

⁴HIV services, Royal Free Hospital, Royal Free London NHS Foundation Trust, London, UK

⁵UCL Respiratory, Division of Medicine, University College London, London, UK

⁶Respiratory Medicine, Royal Free Hospital, Royal Free London NHS Foundation Trust, London, UK

⁷Centre for Clinical Research in Infection and Sexual Health, Institute for Global Health, University College London, London, UK

Correspondence

Nicholas Bakewell, Institute for Global Health, University College London, London NW3 2PF, UK.
Email: n.bakewell@ucl.ac.uk

Abstract

Objectives: Despite improvements in survival of people with HIV admitted to the intensive care unit (ICU), late diagnosis continues to contribute to in-ICU mortality. We quantify the population attributable fraction (PAF) of in-ICU mortality for recent late diagnosis among people with HIV admitted to a London ICU.

Methods: Index ICU admissions among people with HIV were considered from 2000 to 2019. Recent late diagnosis was a CD4 T-cell count < 350 cells/ μ L and/or AIDS-defining illness at/within 6 months prior to ICU admission. Univariate comparisons were conducted using Wilcoxon rank-sum/Cochran–Armitage/ χ^2 /Fisher's exact tests. We used Poisson regression (robust standard errors) to estimate unadjusted/adjusted (age, sex, calendar year of ICU admission) risk ratios (RRs) and regression standardization to estimate the PAF.

Results: In all, 207 index admissions were included [median (interquartile range) age: 46 (38–53) years; 72% male]; 58 (28%) had a recent late diagnosis, all of whom had a CD4 count < 350 cells/ μ L, and 95% had advanced HIV (CD4 count < 200 cells/ μ L and/or AIDS at admission) as compared with 57% of those who did not have a recent late diagnosis ($p < 0.001$). In-ICU mortality was 27% (55/207); 38% versus 22% in those who did and did not have a recent late diagnosis, respectively ($p = 0.02$). Recent late diagnosis was independently associated with increased in-ICU mortality risk (adjusted RR = 1.75) (95% confidence interval: 1.05–2.91), with 17.08% (16.04–18.12%) of deaths being attributable to this.

Conclusions: There is a need for improved public health efforts focused on HIV testing and reporting of late diagnosis to better understand potentially missed opportunities for earlier HIV diagnosis in healthcare services.

Robert F. Miller and Caroline A. Sabin Joint senior authors.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *HIV Medicine* published by John Wiley & Sons Ltd on behalf of British HIV Association.

KEYWORDS

HIV, intensive care unit, late diagnosis, mortality, population attributable fraction

INTRODUCTION

It has been over a decade since the consensus definition of late HIV diagnosis was published in *HIV Medicine*, with this being defined as a CD4 T-cell count < 350 cells/ μ L or having an AIDS-defining event regardless of CD4 count at the time of HIV diagnosis [1]. This definition has enabled comparable longitudinal monitoring and evaluation of public health initiatives aimed at earlier HIV diagnosis and initiation of combination antiretroviral therapy (cART) [2–5]. Despite this, 42% of all new HIV diagnoses in England were made late in 2020, increasing the risk of potentially preventable mortality, morbidity and onward transmission [6–8].

Previous studies have reported that late diagnosis is associated with an increased risk of requiring specialist care and intensive care unit (ICU) admission while in hospital, often due to advanced immunosuppression and disease progression [9–11]. Consequently, those diagnosed late tend to have higher rates of secondary/tertiary healthcare utilization, and thus direct medical costs to healthcare systems primarily due to in-patient costs [12–14].

It is important to quantify the potentially preventable deaths among people with HIV in the ICU that are attributable to late diagnosis, as late diagnosis is an acknowledged risk factor for in-ICU mortality [15]. These data may be used to inform public health efforts aimed at earlier HIV diagnosis in all healthcare services, including ICUs [16]. Previous studies have analysed in-hospital and/or in-ICU mortality outcomes among people with HIV [17–20] and have estimated the attributable risk of mortality to late diagnosis in general populations of people with HIV [21–25]. However, there are no studies that have quantified the population attributable fraction (PAF) of in-ICU mortality to late diagnosis.

Thus, the aim of this study was to estimate the risk of in-ICU mortality associated with and attributable to a recent late diagnosis in the period leading up to ICU admission using data from a cohort of people with HIV admitted to the Royal Free Hospital (RFH; London, UK) ICU between 2000 and 2019.

METHODS**Study design and participants**

We analysed data from electronic health records of unselected people with HIV (≥ 18 years old) admitted to the

RFH ICU between 1 January 2000 and 31 December 2019.

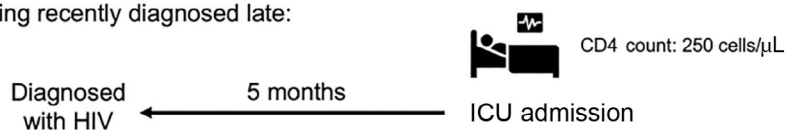
The RFH's Freenet ICU information system was used to obtain data on ICU admissions, including underlying diagnosis requiring ICU admission. RFH's ICU Intensive Care National Audit & Research Centre (ICNARC) submission records over the study period were used to obtain data on patient characteristics measured at ICU admission, including sex (at birth), age and Acute Physiology and Chronic Health Evaluation (APACHE II) score. The RFH WinPath (CliniSys, Chertsey, UK) blood results system, supplemented by the ICU discharge summary documentation available on Freenet ICU, was used to obtain data on the date of HIV-1 infection diagnosis, CD4 count (cells/ μ L), HIV-1 viral load (VL) (RNA copies/mL) and cART status.

Variable definitions

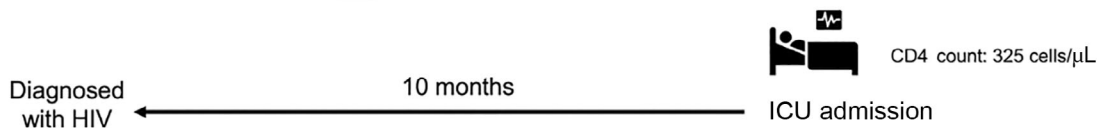
In the absence of data on CD4 count at HIV diagnosis, and as our primary interest was in people who were diagnosed late just prior to or at ICU admission in whom the risk of mortality would be expected to be particularly high [21, 26], we retrospectively identified individuals with an HIV diagnosis within 6 months of their index ICU admission and where the person had (1) a CD4 count < 350 cells/ μ L at ICU admission, and/or (2) an underlying diagnosis requiring ICU admission that was an AIDS-defining illness as defined by US Centers for Disease Control and Prevention (CDC) [27] regardless of CD4 count (Figure 1). Individuals who did not meet these criteria were considered not to have a recent late diagnosis, as were those with missing data on CD4 count but with a HIV diagnosis date more than 6 months prior to ICU admission, or missing data on HIV diagnosis date but with a CD4 count ≥ 350 cells/ μ L. Those with missing data on both HIV diagnosis date and CD4 count, an HIV diagnosis date in the 6 months prior to ICU admission and missing CD4 count, or a CD4 count < 350 cells/ μ L and missing HIV diagnosis date were excluded from the primary analysis, as we could not be certain of their recent late diagnosis classification. However, those excluded were included in sensitivity analyses as described in the following.

People were classified as having advanced HIV at admission if they had a CD4 count < 200 cells/ μ L and/or an AIDS-defining illness. People were classified as having

Example patient defined as being recently diagnosed late:



Example patient defined as being **not** recently diagnosed late:



Exclusions due to indeterminable *recent late diagnosis* classification:

Scenario 1	Scenario 2	Scenario 3
Missing data on both HIV diagnosis date and CD4 count	HIV diagnosis date in the 6 months prior to ICU admission but missing data on CD4 count	CD4 count < 350 cells/μL but missing HIV diagnosis date

FIGURE 1 Schematic defining recent late diagnosis retrospectively from ICU admission

an undetectable VL if their VL was ≤ 50 copies/mL at ICU admission. Lastly, people were classified as taking any form of cART if they had (1) data on cART start date pre-dating ICU admission; or (2) a VL < 1000 copies/mL at ICU admission but no cART date, as it was considered unlikely that these patients exhibiting viraemic control were not on any form of cART.

Statistical analyses

We summarized data on patient characteristics and outcomes collected at ICU admission by recent late diagnosis group using counts (proportions) for categorical variables and medians [interquartile ranges (IQRs)] for continuous variables; univariate comparisons were conducted using Wilcoxon rank-sum, χ^2 and Fisher's exact tests, as appropriate. The Cochran–Armitage test was used to test for a difference in (linear) trend between late diagnosis groups across five 4-year groups based on ICU admission date over the 20-year study period.

We estimated the unadjusted and adjusted relative risk of in-ICU mortality (i.e. outcome) comparing the two recent late diagnosis groups in terms of risk ratios (RRs) using Poisson regression fitted with robust standard errors [28]. Adjusted analyses included: linear calendar year of ICU admission date (continuous), age (continuous) and sex (binary). We did not adjust for clinical factors such as APACHE II score, advanced HIV and/or undetectable VL, as we considered these variables to be

strongly influenced by a recent late diagnosis and thus adjustment for them would remove the association of interest.

Following Poisson regression, regression standardization was used to estimate unadjusted and adjusted PAFs of in-ICU mortality for recent late diagnosis. The PAF was of interest because it quantifies the proportion of in-ICU deaths in our total study population that can be attributed to recent late diagnosis. We followed the Greenland and Drescher method for cohort studies to estimate the PAF [29]; this approach has been applied using regression standardization [30]. We used the `stdReg` package in R to compute Wald-type confidence intervals (CIs) for the PAF using the delta method [31].

Sensitivity analyses

Bootstrap CIs (bsCIs; bias-corrected and accelerated method) based on 1000 bootstrap replicates were calculated for the PAF, as the asymptotic normality assumption of the Wald-type CIs might not be met given our relatively small sample size.

To assess the sensitivity of results when considering all patients who died in hospital, not only in the ICU, we conducted an analysis on the attributable risk of in-hospital mortality to recent late diagnosis and estimated the PAF. In addition, to assess the sensitivity of results to missing data in the exposure, we conducted a multiple imputation analysis using the Substantive Model

Compatible Fully Conditional Specification approach under a missing at random assumption [32]. Further details are provided in the Appendix S1.

All analyses were performed using R version 4.1.0, with two-sided p -values < 0.05 considered to be statistically significant [33].

Ethics

This project was registered as a clinical audit with RFH in July 2020 and confirmed to be an audit by RFH Research and Innovation in October 2021. All data collected were anonymized at the point of capture.

RESULTS

Patient characteristics

Of the 221 people with HIV (≥ 18 years old) admitted to ICU over the 20-year study period, 207 were included in the primary analyses (index admission only). At ICU admission, the median (IQR) age of patients was 46 (38–53) years, most (72%) were male, a relatively large proportion of admission diagnoses were lower respiratory tract [31%; e.g. *Pneumocystis jirovecii* pneumonia (PCP)] or other infections (13%; e.g. septic shock), the median (IQR) APACHE II score was moderately high at 19 (14–25), and the number of admissions was highest in 2016–2019 ($n = 59$). For HIV-specific characteristics measured at ICU admission, the median (IQR) time since HIV diagnosis was 6 (0–14) years, two-thirds had advanced HIV (67%), 45% had an undetectable VL (≤ 50 copies/mL), the median (IQR) CD4 count was low at 122 (29–297) cells/ μL , and 74% were receiving cART (or 53% overall had data available on cART start date) (Table 1).

Over one-quarter (28%, 58/207) had a recent late diagnosis, of whom 10 (17%) were diagnosed at ICU admission [vs. 1 (1%) of those not recently diagnosed late; $p < 0.001$], all had a CD4 count < 350 cells/ μL and most (95%) had advanced HIV (vs. 57% of those not recently diagnosed late with advanced HIV; $p < 0.001$). Among the 149 people without a recent late diagnosis, 10 either had a CD4 count ≥ 350 cells/ μL and a missing HIV diagnosis date ($n = 7$) or an HIV diagnosis more than 6 months prior to ICU admission and a missing CD4 count ($n = 3$); two were diagnosed with HIV within 6 months of ICU admission but with a CD4 count ≥ 350 cells/ μL (no AIDS-defining illness); and the remaining 137 were diagnosed more than 6 months prior to admission (106 with a CD4 count < 350 cells/ μL , 31 with a CD4 count ≥ 350 cells/ μL). There were no statistically

significant differences between the two groups for median age [44 years (recently diagnosed late) vs. 46 years (not recently diagnosed late); $p = 0.11$], the proportion who were male (66% vs. 74%; $p = 0.23$), median APACHE II score (21 vs. 19; $p = 0.28$), and the distribution of main diagnosis category ($p = 0.14$) and year of admission ($p = 0.81$). However, as expected, those recently diagnosed late tended to include fewer people with an undetectable VL (9% vs. 58%; $p < 0.001$) and they were less likely to be receiving cART (33% vs. 88%; $p < 0.001$) [or to have data available on cART start date (14% vs. 68%; $p < 0.001$)] (Table 1).

Clinical outcomes

Overall, the median (IQR) length of stay was 5 (2–12) days and 27% died in ICU. Those recently diagnosed late had a higher median length of stay (6 vs. 4 days; $p = 0.02$) and a higher proportion of patients who died in ICU (38% vs. 22%; $p = 0.02$) (Table 1). Before adjustment, it was estimated that those recently diagnosed late had a 71% higher risk of in-ICU mortality compared with those not recently diagnosed late [crude RR = 1.71 (95% CI: 1.10–2.68)]. After adjustment for age, sex and calendar year (of ICU admission date), this estimate was slightly amplified to 75% [adjusted RR = 1.75 (95% CI: 1.05–2.91)] and recent late diagnosis was independently associated with in-ICU mortality (Table 2).

Using regression standardization and considering the total study ICU population of people with HIV, it was estimated that nine of the 55 in-ICU deaths [or 16.64% (95% CI: 15.60–17.69), i.e. PAF] can be attributed to recent late diagnosis before adjustment for potential confounders. After adjustment for age, sex and calendar year, the estimated PAF was similar at 17.08% (95% CI: 16.04–18.12), or nine of the 55 in-ICU deaths being attributable to recent late diagnosis (Table 2).

The calculated 95% bsCIs based on 1000 bootstrap replicates were much wider than Wald-type CIs before (95% bsCI: 2.59–33.51) and after (95% bsCI: 2.81–33.18) adjustment, but the conclusions remained the same. Findings considering in-hospital mortality as the outcome and after multiple imputation were consistent with the results summarized earlier; however, primarily for the multiple imputation analysis, the point estimates were attenuated and the CIs were wider (see Appendix S1).

DISCUSSION

We aimed to quantify the risk of in-ICU mortality among people with HIV associated with and attributable to late

TABLE 1 Summary of patient characteristics, year of admission and clinical outcomes

Characteristic [<i>n</i> (%) or median (IQR)]	Overall (<i>n</i> = 207)	Not recently diagnosed late (<i>n</i> = 149)	Recently diagnosed late (<i>n</i> = 58)	<i>p</i> -value
Demographic factors				
Age (years)	46 (38–53)	46 (40–54)	44 (36–52)	0.11
Male (sex at birth)	148 (71.5%)	110 (73.8%)	38 (65.5%)	0.23
Clinical factors				
APACHE II	19 (14–25)	19 (13–25)	21 (14–26)	0.28
Missing	10	6	4	
Advanced HIV ^a	138 (67.3%)	83 (56.5%)	55 (94.8%)	< 0.001
Missing	2	2	0	
Undetectable (VL ≤ 50 copies/mL)	90 (45.0%)	85 (58.2%)	5 (9.3%)	< 0.001
Missing	7	3	4	
CD4 count at admission	122 (29–297)	190 (64–380)	32 (12–83)	< 0.001
Missing	3	3	0	
Receipt of cART	147 (73.5%)	129 (88.4%)	18 (33.3%)	< 0.001
Available cART start date ^d	109 (52.7%)	101 (67.8%)	8 (13.8%)	< 0.001
Missing	7	3	4	
Time since HIV diagnosis (days)	1996 (67–4997)	3303 (1648–6322)	24 (3–47)	< 0.001
Missing	7	7	0	
Primary diagnosis at admission category				
Cardiovascular	7 (3.4%)	6 (4.0%)	1 (1.7%)	0.14
Gastrointestinal	23 (11.1%)	18 (12.1%)	5 (8.6%)	
Infection	27 (13.0%)	18 (12.1%)	9 (15.5%)	
Lower respiratory tract infection	65 (31.4%)	43 (28.9%)	22 (37.9%)	
Neurological	20 (9.7%)	12 (8.1%)	8 (13.8%)	
Oncological/haematological	18 (8.7%)	11 (7.4%)	7 (12.1%)	
Renal	12 (5.8%)	10 (6.7%)	2 (3.4%)	
Other ^b	35 (16.9%)	31 (20.8%)	4 (6.9%)	
Year of admission^c				
2000–2003	19 (9.2%)	14 (9.4%)	5 (8.6%)	0.81
2004–2007	42 (20.3%)	26 (17.4%)	16 (27.6%)	
2008–2011	43 (20.8%)	37 (24.8%)	6 (10.3%)	
2012–2015	44 (21.3%)	33 (22.1%)	11 (19.0%)	
2016–2019	59 (28.5%)	39 (26.2%)	20 (34.5%)	
Clinical outcomes				
Length of stay (days)	5 (2–12)	4 (2–12)	6 (3–17)	0.02
Died in ICU	55 (26.6%)	33 (22.1%)	22 (37.9%)	0.02

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; cART, combination antiretroviral therapy; IQR, interquartile range; VL, viral load; ICU, intensive care unit.

^aCD4 count < 200 cells/μL and/or an AIDS-defining illness at admission.

^bThe “other” category primarily includes those recovering from operation [22/35 (62.9%)]. There were 7/35 (20.0%) patients with an intentional drug overdose; and it is important to note that no patients had an immune reconstitution inflammatory syndrome (IRIS)-related diagnoses.

^c*p*-value is based on a Cochran–Armitage test for linear trend using the 4-year groups, not single calendar years.

^dWhether or not a patient has a cART start date available regardless of VL (no missing data on this variable, while there is missing data when determining receipt of cART considering VL as well).

TABLE 2 Unadjusted and adjusted results from the Poisson regression (robust standard errors) and regression standardization analyses (complete case analysis)

Parameter	Crude	Adjusted age + sex + linear calendar year		
	Estimate (95% CI)	p-value	RR (95% CI)	p-value
(a) RR, recent late diagnosis				
No	Ref.		Ref.	
Yes	1.71 (1.10–2.68)	0.02	1.75 (1.05–2.91)	0.03
(b) PAF of in-ICU mortality for recent late diagnosis				
PAF (%) – Wald-type CIs	16.64 (15.60–17.69)	–	17.08 (16.04–18.12)	–
PAF (%) – bootstrap CIs	16.64 (2.59–33.51)	–	17.08 (2.81–33.18)	–

Abbreviations: CI, confidence interval; RR, risk ratio; PAF, population attributable fraction.

diagnosis within 6 months prior to or at ICU admission. We estimated that in an already critically ill population of people with HIV, those with a recent late diagnosis had a 75% higher risk of in-ICU mortality relative to those who did not have a recent late diagnosis; and 17% of in-ICU deaths could have potentially been prevented if these recent late diagnoses had been avoided, adjusting for age, sex and calendar year of ICU admission. This means that approximately nine of the 55 deaths potentially could have been avoidable in this population of people with HIV admitted to the RFH ICU between 2000 and 2019. Although this number may seem modest, this result highlights that even in a population of people with HIV admitted to the ICU with an already poor prognosis, in-ICU mortality continues to be attributable to recent late diagnosis, a preventable risk factor for in-ICU mortality that may be avoidable by earlier HIV testing and diagnosis.

The persistent problem of late diagnosis and its association with an increased risk of mortality among people with HIV in general is well documented [8, 21, 22, 34–37]. A 10-year study using data collected between 1999 and 2008 from a national cohort of people with HIV in England and Wales estimated that 60% of all-cause mortality was attributable to late diagnosis [38]. Another study in Singapore that used data collected between 2012 and 2016 from a cohort of their population of people with HIV estimated that 78% of short-term mortality was attributable to late diagnosis [23]. These previous studies on general populations of people with HIV are informative and our findings are consistent with these studies in relation to late diagnosis generally being associated with an increased risk of mortality and resulting in potentially avoidable excess deaths. However, our findings are not directly comparable to these previous studies that used data collected from general populations of people with HIV, and our estimated PAF of in-ICU mortality for recent late diagnosis is markedly lower than the estimates of the previous studies

noted. We believe this is because our total study population comprises people with HIV with an already poor prognosis that required admission to ICU, and our study outcome is specific to in-ICU mortality.

When considering studies specific to ICU populations of people with HIV, it is evident that these people are now presenting to care with non-AIDS-related events, and short-term mortality has markedly improved in these populations, often owing to advances in ICU clinical practices and better access to cART [10, 39–42]. We recently presented findings using data from the same cohort as in this paper that provide further evidence of a marked improvement in in-hospital and in-ICU survival among people with HIV since 2000 [43]. Despite this, the number of ICU admissions for people with HIV has remained relatively stable [44].

Late diagnosis remains a major risk factor for both ICU mortality and ICU admission, where it has been reported that people diagnosed late have a nearly nine-fold increased risk of ICU admission compared with those not diagnosed late [9, 15]. In our present study, 28% of people admitted to ICU were diagnosed late within 6 months prior to or at their index ICU admission. There was no statistically significant reduction in the proportion recently diagnosed late over the study period (2000–2019), although it varied over this time, increasing from 26% in 2000–2003 to 34% in 2016–2019. Most of those with a recent late diagnosis presented to ICU with advanced HIV, a primary diagnosis of lower respiratory tract (e.g. PCP) or other infection (e.g. septic shock), a detectable VL (> 50 copies/mL) and severe immunosuppression based on CD4 count. The clinical characteristics of those with a recent late diagnosis are unsurprising, as a high proportion of opportunistic infections such as PCP and advanced HIV among patients with a recent HIV diagnosis presenting to ICU has been reported previously [18]. The median length of stay was higher for those recently diagnosed late (6 vs. 4 days), indirectly

suggesting greater ICU utilization and, thus, likely higher medical costs among this group. This aligns with previous studies that reported higher healthcare utilization and medical costs among those diagnosed late [12, 13, 45]. The proportion who died in the ICU among those recently diagnosed late in our study population (38%) is comparable to two previous studies in the UK that reported the in-ICU mortality of patients with newly diagnosed HIV after hospitalization and who were also all probably diagnosed late, where estimates were 31% [17] and 26% [46]. The proportion in our study is possibly higher because we considered diagnoses within 6 months prior to or at ICU admission. However, care is also needed when comparing our results with other ICU-/hospital-based studies, as the differences could also be due to differences in the time period(s) examined, patient demographics, and ICU admission criteria and clinical practice. Furthermore, our focus on recent late diagnosis means that our PAF may be underestimated if those diagnosed late more than 6 months before admission continue to experience poor ICU mortality outcomes.

Although the previous studies summarized above have shown that in-ICU mortality can be linked to recent late diagnosis, we did not identify any studies on in-ICU mortality that specifically quantified comparable measures of risk of in-ICU mortality. Therefore, although our data may be perceived as largely confirmatory that people diagnosed late have an increased risk of in-ICU mortality, the quantification of the ICU population impact of recent late diagnosis using the PAF is a unique feature of our work. In this context, the results of our study also indicate that there is a need for public health interventions aimed at scaling up access to and uptake of HIV testing in primary and secondary healthcare services (including prior to the escalation of care to ICU) to help ensure prompt recognition and treatment of HIV and thus prevent the progression to critical illness. Such interventions would aid in reducing the proportion of those diagnosed late being admitted to ICU, and thus in reducing medical costs; and, most importantly, avoid potentially preventable in-ICU deaths. Additionally, with no notable decline in the ICU admission rate of people with HIV and the increased risk of ICU admission and mortality among those diagnosed late, it is important to continue to involve infectious disease specialists early when providing critical care to people with HIV.

One area of research that requires further study that we were not able to explore due to data limitations is the occurrence of missed opportunities for HIV testing among those admitted to ICU who are diagnosed late. The British HIV Association (BHIVA) Standards of Care recommends that a critical case (or 'look back') review be conducted to better understand whether missed opportunities for HIV testing

were likely [47]. Previous studies have reported that around 60% of people diagnosed late experience missed opportunities for HIV testing, with most occurring in non-specialist primary care settings [11, 48]. However, there are many missed opportunities for HIV testing that occur among people admitted to hospital. It has been reported that only about 5% of patients admitted to a large UK ICU who qualified for HIV testing according to UK HIV testing guidelines were tested, of whom approximately 7% tested positive [49]. Therefore, we encourage future studies to obtain data on look-back reviews conducted in ICU populations to better understand missed opportunities for HIV testing. This may identify the most appropriate care settings on which to focus HIV testing initiatives in this population of critically ill people with HIV, to ensure earlier HIV diagnosis and timely entry into the HIV care pathway, as well to avoid potential preventable deaths.

A key strength of our work is that it is the first study to provide an estimate of PAF of in-ICU mortality for recent late diagnosis among people with HIV admitted to ICU using data from a cohort at a large hospital in London, UK, over a 20-year period. Another strength is that we conducted a sensitivity analysis on missing data in the exposure to ensure robustness of our results to potential bias due to missingness.

However, our study is not without its limitations. ICU admission was not protocolized and based on the discretion of the on-call intensivist for a particular day of admission over the study period, and thus the likely existence of varying clinical and/or physiological thresholds for admission introduced selection/sampling bias. This has probably biased the results towards the null compared with studies on attributable risk of all-cause mortality to late diagnosis in general populations of people with HIV. This is probably because our study population was likely to have a higher proportion of deaths among those not recently diagnosed late than would be observed in the general population of people with HIV. Thus, this limits the generalizability of our findings to other populations of people with HIV and mortality in general. We note that our analyses, which are based on a population of people admitted to ICU, will not capture any deaths following late diagnosis that are not associated with an ICU admission. Additionally, this is a single-centre study conducted in an ICU at a hospital experienced in HIV care with a relatively small sample size, limiting both the power and the generalizability of the results to other ICU populations of people with HIV. Although data were not retrievable from additional hospitals/centres for this study, we suggest that future studies explore the possibility of including data from multiple hospitals/centres.

Furthermore, we retrospectively classified a recent late diagnosis as one that occurred within 6 months prior

to or at ICU admission. We recognize that this does not exactly align with the consensus definition that classifies late diagnosis based on a CD4 count < 350 cells/ μ L or presentation to care with an AIDS-defining illness at or near the HIV diagnosis date. However, historic information on CD4 counts at the time of HIV diagnosis may often be unavailable to those providing care to people with HIV admitted to ICU. Given that the highest mortality risk associated with late diagnosis has been reported to be during the first 6–12 months, we used a modified definition of ‘recent late diagnosis’ to provide a pragmatic definition that would have clinical relevance to the ICU care setting. The results of our study rely on the assumption of no unmeasured confounding. We were not able to account for important confounders such as acquisition risk, drug use, ethnicity/race, immigration status and socioeconomic status. We acknowledge that we cannot rule out the possibility that a combination of unmeasured confounders could explain away the effect of late diagnosis. Therefore, we recommend that future studies retrieve data on potential confounders not accounted for in our study. Lastly, the results also rely on the accuracy of the observed covariates gathered from retrospective data sources.

CONCLUSIONS

The results from this analysis estimated that a recent late diagnosis of HIV is associated with an increased risk of in-ICU mortality and that a moderate number of in-ICU deaths among people with HIV admitted to the RFH ICU between 2000 and 2019 can be attributed to recent late diagnosis within 6 months prior to or at ICU admission. These deaths could have potentially been avoided by earlier HIV testing, diagnosis and cART initiation. Our findings further support the need for improved public health efforts focused on earlier HIV testing and diagnosis to prevent the progression of HIV resulting in critical illness and potentially avoidable deaths in the ICU due to late diagnosis in an era of highly effective cART and advancements in clinical practice and diagnostic technology. Additionally, further research is needed on the characterization of missed opportunities for HIV testing among people with HIV admitted to ICU.

AUTHOR CONTRIBUTIONS

RFM, TK and CAS conceptualized this study, with RFM and TK collating the datasets. NB carried out the statistical analyses under the supervision of CAS and developed the initial draft of the manuscript. All authors provided critical feedback and helped to shape the final analyses and manuscript.

ACKNOWLEDGEMENTS

The authors are grateful for the contributions of the RFH ICU Data Management Team, including Dr Mark de Neef, Dr Nazri Unn and Peggy Tsang. The authors are also grateful for the contributions of the HIV Data Management Team, led by Alan Hunter. NB was funded through the National Institute for Health and Care Research Health Protection Research Unit (NIHR HPRU) in Blood Borne and Sexually Transmitted Infections at University College London in partnership with the UK Health Security Agency. The views expressed are those of the authors and not necessarily those of the NIHR, the Department of Health and Social Care or the UKHSA. We also acknowledge members of the NIHR HPRU in Blood Borne and Sexually Transmitted Infections Steering Committee: C. Sabin (HPRU Director), J. Saunders (UKHSA Lead), C. Mercer, H. Mohammed, G. Rait, R. Simmons, W. Rosenberg, T. Mbisa, R. Raine, S. Mandal, R. Yu, S. Ijaz, F. Lorencatto, R. Hunter and K. Foster, M. Tahir.

DATA AVAILABILITY STATEMENT

The data used in this study cannot be shared publicly as they are protected health data; the information is personal or special category personal data, and there is risk of “re-identification” of data that have been pseudonymized. Access to protected health data is subject to robust governance protocols, where it is lawful, ethical and safe to do. Access to protected health data is always strictly controlled using legally binding data-sharing contracts.

ORCID

Caroline A. Sabin  <https://orcid.org/0000-0001-5173-2760>

REFERENCES

1. Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med.* 2011;12(1): 61-64.
2. Darcis G, Lambert I, Sauvage A-S, et al. Factors associated with late presentation for HIV care in a single Belgian reference center: 2006–2017. *Sci Rep.* 2018;8(1):1-6.
3. EuroSIDA LPWGi, dk CKglr. Estimating the burden of HIV late presentation and its attributable morbidity and mortality across Europe 2010–2016. *BMC Infect Dis.* 2020;20:1-11.
4. Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the collaboration of observational HIV epidemiological research Europe study (COHERE). *PLoS Medicine.* 2013;10(9):e1001510.
5. Miranda MN, Pingarilho M, Pimentel V, et al. Determinants of HIV-1 late presentation in patients followed in Europe. *Pathogens.* 2021;10(7):835.
6. Lester J, Martin V, Shah A, et al. HIV Testing, PrEP, new HIV Diagnoses, and Care Outcomes for People Accessing HIV Services: 2022 report. *The annual official statistics data release*

- (data to end of December 2021). UK Health Security Agency; 2022.
7. Bath RE, Emmett L, Verlander NQ, Reacher M. Risk factors for late HIV diagnosis in the east of England: evidence from national surveillance data and policy implications. *Int J STD AIDS*. 2019;30(1):37-44.
 8. May M, Gompels M, Delpuch V, et al. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK collaborative HIV cohort (UK CHIC) study. *BMJ*. 2011;343:343.
 9. Shrobbree J, Campbell LJ, Ibrahim F, et al. Late HIV diagnosis is a major risk factor for intensive care unit admission in HIV-positive patients: a single Centre observational cohort study. *BMC Infect Dis*. 2013;13(1):1-7.
 10. Barbier F, Mer M, Szychowiak P, et al. Management of HIV-infected patients in the intensive care unit. *Intensive Care Med*. 2020;46(2):329-342.
 11. Wohlgenut J, Lawes T, Laing R. Trends in missed presentations and late HIV diagnosis in a UK teaching hospital: a retrospective comparative cohort study. *BMC Infect Dis*. 2012;12(1):1-10.
 12. Fleishman JA, Yehia BR, Moore RD, Gebo KA, Network HR. The economic burden of late entry into medical care for patients with HIV infection. *Med Care*. 2010;48(12):1071-1079.
 13. Guaraldi G, Zona S, Menozzi M, et al. Late presentation increases risk and costs of non-infectious comorbidities in people with HIV: an Italian cost impact study. *AIDS Res Ther*. 2017;14(1):1-7.
 14. O'Connell S, Enkelmann J, Sadlier C, Bergin C. Late HIV presentation—missed opportunities and factors associated with a changing pattern over time. *Int J STD AIDS*. 2017;28(8):814-821.
 15. Arancibia FEAM. AIDS patients in the ICU. *Infection Control in the Intensive Care Unit*. Springer; 2011.
 16. Thornhill J, Mandersloot G, Bath R, Orkin C. Opt-out HIV testing in adult critical care units. *Lancet*. 2014;383(9927):1460.
 17. Adlakha A, Pavlou M, Walker D, et al. Survival of HIV-infected patients admitted to the intensive care unit in the era of highly active antiretroviral therapy. *Int J STD AIDS*. 2011;22(9):498-504.
 18. Akgun KM, Huang L, Morris A, Justice AC, Pisani M, Crothers K. Critical illness in HIV-infected patients in the era of combination antiretroviral therapy. *Proc Am Thorac Soc*. 2011;8(3):301-307.
 19. Laher A, Paruk F, Venter W, Ayeni O, Richards G. Predictors of in-hospital mortality among HIV-positive patients presenting with an acute illness to the emergency department. *HIV Med*. 2021;22(7):557-566.
 20. Maphula R, Laher A, Richards G. Patterns of presentation and survival of HIV-infected patients admitted to a tertiary-level intensive care unit. *HIV Med*. 2020;21(5):334-341.
 21. Chadborn TR, Delpuch VC, Sabin CA, Sinka K, Evans BG. The late diagnosis and consequent short-term mortality of HIV-infected heterosexuals (England and Wales, 2000–2004). *Aids*. 2006;20(18):2371-2379.
 22. Sobrino-Vegas P, Moreno S, Rubio R, et al. Impact of late presentation of HIV infection on short-, mid-and long-term mortality and causes of death in a multicenter national cohort: 2004–2013. *J Infect*. 2016;72(5):587-596.
 23. Ang LW, Toh MPH, Wong CS, et al. Short-term mortality from HIV-infected persons diagnosed from 2012 to 2016: impact of late diagnosis of HIV infection. *Medicine*. 2021;100(26):e26507.
 24. Hønge BL, Jespersen S, Aunsborg J, et al. High prevalence and excess mortality of late presenters among HIV-1, HIV-2 and HIV-1/2 dually infected patients in Guinea-Bissau—a cohort study from West Africa. *Pan Afr Med J*. 2016;25:25.
 25. Belaunzarán-Zamudio PF, Caro-Vega YN, Shepherd BE, et al. The population impact of late presentation with advanced HIV disease and delayed antiretroviral therapy in adults receiving HIV care in Latin America. *Am J Epidemiol*. 2020;189(6):564-572.
 26. Chadborn TR, Baster K, Delpuch VC, et al. No time to wait: how many HIV-infected homosexual men are diagnosed late and consequently die?(England and Wales, 1993–2002). *Aids*. 2005;19(5):513-520.
 27. Prevention UCfDCA. Appendix A: AIDS-Defining Conditions. December 2008.
 28. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.
 29. Greenland S, Drescher K. Maximum likelihood estimation of the attributable fraction from logistic models. *Biometrics*. 1993;49:865-872.
 30. Sjölander A. Estimation of causal effect measures with the R-package `stdReg`. *Eur J Epidemiol*. 2018;33(9):847-858.
 31. Sjolander A, Dahlqwist E. `stdReg: Regression Standardization`. R package version 3.4.1. 2021. <https://CRAN.R-project.org/package=stdReg>
 32. Bartlett JW, Seaman SR, White IR, Carpenter JR, Initiative* AsDN. Multiple imputation of covariates by fully conditional specification: accommodating the substantive model. *Stat Methods Med Res*. 2015;24(4):462-487.
 33. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2022.
 34. Brown AE, Kall MM, Smith RD, Yin Z, Hunter A, Delpuch VC. Suppl 1: auditing national HIV guidelines and policies: the United Kingdom CD4 surveillance scheme. *Open AIDS J*. 2012;6:149-155.
 35. Fisher M. Late diagnosis of HIV infection: major consequences and missed opportunities. *Curr Opin Infect Dis*. 2008;21(1):1-3.
 36. Lee MJ, Curtis H, van Halsema C, Chadwick DR. Evaluating a pilot process for reviewing late HIV diagnoses in England and Wales. *Clin Med*. 2020;20(2):189-195.
 37. EuroCoord LPWGiCi. Late presentation for HIV care across Europe: update from the collaboration of observational HIV epidemiological research Europe (COHERE) study, 2010 to 2013. *Eurosurveillance*. 2015;20(47):30070.
 38. Simmons R, Ciancio B, Kall M, Rice B, Delpuch V. Ten-year mortality trends among persons diagnosed with HIV infection in England and Wales in the era of antiretroviral therapy: AIDS remains a silent killer. *HIV Med*. 2013;14(10):596-604.
 39. Akgün KM, Pisani M, Crothers K. The changing epidemiology of HIV-infected patients in the intensive care unit. *J Intensive Care Med*. 2011;26(3):151-164.
 40. Azoulay É, de Castro N, Barbier F. Critically ill patients with HIV: 40 years later. *Chest*. 2020;157(2):293-309.
 41. Coquet I, Pavie J, Palmer P, et al. Survival trends in critically ill HIV-infected patients in the highly active antiretroviral therapy era. *Crit Care*. 2010;14(3):1-9.

42. Ford N, Patten G, Rangaraj A, Davies M-A, Meintjes G, Ellman T. Outcomes of people living with HIV after hospital discharge: a systematic review and meta-analysis. *Lancet HIV*. 2022;9(3):e150-e159.
43. Kanitkar T, Dissanayake O, Bakewell N, et al. Improving short-term mortality of people living with HIV admitted to the intensive care unit: a 20-year study (2000-2019). *HIV MEDICINE*. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2022:6-7.
44. Turvey SL, Bagshaw SM, Eurich DT, Sliagl WI. Epidemiology and outcomes in critically ill patients with human immunodeficiency virus infection in the era of combination antiretroviral therapy. *Can J Infect Dis Med Microbiol*. 2017;2017:1-9.
45. Krentz HB, Gill MJ. The direct medical costs of late presentation (< 350/mm³) of HIV infection over a 15-year period. *AIDS Res Treat*. 2012, The Direct Medical Costs of Late Presentation (<350/mm³) of HIV Infection over a 15-Year Period;2012:1-8.
46. Dickson SJ, Batson S, Copas A, Edwards SG, Singer M, Miller RF. Survival of HIV-infected patients in the intensive care unit in the era of highly active antiretroviral therapy. *Thorax*. 2007;62(11):964-968.
47. Association BH. *Standards of Care for People Living with HIV 2013*. British HIV Association; 2012.
48. Horsley Downie J, Pegler M, Widdrington J, Price D, Premchand N, Chadwick D. Late HIV diagnosis and missed opportunities for testing: piloting a standardised, multi-source review process. *Int J STD AIDS*. 2020;31(3):208-213.
49. Dodd MC, Collini PJ, Dockrell DH. Low concordance with HIV testing guidelines in a retrospective review of intensive care practice. *Thorax*. 2013;68(11):1072-1074.
50. Barnard J, Rubin DB. Miscellaneous. Small-sample degrees of freedom with multiple imputation. *Biometrika*. 1999;86(4): 948-955.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bakewell N, Kanitkar T, Dissanayake O, et al. Estimating the risk of mortality attributable to recent late HIV diagnosis following admission to the intensive care unit: A single-centre observational cohort study. *HIV Med*. 2022;1-10. doi:10.1111/hiv.13436