Risk factors for loss to follow-up, transfer or death among people living with HIV on their first antiretroviral therapy regimen in Mali

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Running head: Loss to follow-up among PLHIV in Mali.

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Objectives: Risk factors for loss-to-follow-up (LTFU) were assessed for people living with HIV (PLHIV) at various reference outpatient clinics (expertise level II) and hospitals (expertise level III) in Mali.

Methods: HIV-1-positive adults starting antiretroviral therapy (ART) in 2006-2013 were eligible. Risk factors for LTFU, defined as no visit in the six months preceding the last database update, were assessed with Cox model, taking into account the competing risks of transfer and death. Potential risk factors at start of ART were demographic and socioeconomic variables, WHO stage and CD4, period, ART regimen, region of care, expertise level and distance from home.

Results: We included 9,821 PLHIV, 33% male, starting ART at nine outpatient clinics and seven hospitals (5+2 in Bamako and 4+5 in the regions) with a median (IQR) CD4 count of 153/µL (56-270). Five-year cumulative incidences of LTFU, transfer and death were 35.2%, 9.7% and 6.7%, respectively. People followed at Bamako hospitals > 5 km from home, at regional hospitals or at regional outpatient clinics < 5 km from home were at higher risk of LTFU than people followed at Bamako outpatient clinics, whereas people followed at regional outpatient clinics 5-50 km away from home were at lower risk for LTFU. Deaths were less frequent at hospitals, whether in Bamako or the regions, than at Bamako outpatient clinics, and more frequent at regional outpatient clinics.

Conclusions: Expertise level and distance to care were associated with LTFU. Stigmatisation may play a role for PLHIV living close to the centres in the regions.

Introduction

Loss to follow-up (LTFU) is a predictor of poor survival in PLHIV, and is the principal problem in HIV care and in the evaluation of ART access programmes in sub-Saharan Africa [1-3], in which mean attrition rates of 25.0% and 38.4% at 12 and 24 months have been reported respectively, with LTFU accounting for 56% of attrition [4].

In Mali, a West African country with 16.8 million inhabitants, a non-governmental organisation, "Association de Recherche, de Communication et d'Accompagnement à Domicile des personnes vivant avec le VIH/Sida" (ARCAD-SIDA), began to provide healthcare for PLHIV in Bamako (the capital of Mali) in 1998, gradually expanding its activities to several regions after November 2001. Healthcare for PLHIV became free after mid-2004, with support from the Global Fund, "Ensemble pour une Solidarité Thérapeutique Hospitalière en Réseau" (ESTHER), a French agency for AIDS care in developing countries, and the Malian government [5-6]. There were 99,000 adults living with HIV in Mali in 2013, 27,000 of whom were treated [5].

Our aim was to analyse ART outcomes in ESTHER-supported clinical centres after more than ten years of the scaling-up of access to ART, and to assess risk factors for LTFU, transfer to other centres and death, focusing on structural barriers, such as care in the capital or in the regions, care centre expertise level, distance from home to the centre.

Methods

Study setting

In Mali, HIV care and ART are provided by community outpatient clinics (*n*=14) offering consultations with nurses and/or general practitioners (expertise level I), reference outpatient clinics (*n*=54) offering consultations with general practitioners, obstetricians and ophthalmologists, minimal medical tests, including CD4, and simple radiology (level II), or hospitals (*n*=9) offering the same care plus specialized consultations and medical tests, including viral load (VL), and CT scans (level III).

The ESTHER initiative focused on reinforcing the clinical skills of health professionals, simultaneously providing clinical mentoring, teaching, monitoring of CD4, VL and HIV drug resistance. In addition, since 2005, ESTHER has provided an electronic medical records system "Evaluation et Suivi Opérationnel des Programmes d'ESTHER" (ESOPE, Epiconcept, France) for monitoring PLHIV care. This system was progressively implemented at five reference outpatient clinics and two hospitals in Bamako, and at four reference outpatient clinics and five hospitals in five regions (Supplementary figure 1) [6]. The PLHIV included in the ESOPE database accounted for 64% of the 51,000 PLHIV in healthcare for HIV in Mali at the last database update, on March 31st 2015 [7].

Study population

This study included all the HIV-1-positive adults, aged ≥18 years who began ART between January 1st 2006 and December 31st 2013 at one of the 16 care centres contributing to the ESOPE database, thus beginning treatment at least one year before the last database update (31 March 2015), and who returned for their one-month visit. We did not include PLHIV beginning ART before 2006, because the first national guidelines on HIV care and ART were provided at the end of 2005, with subsequent revisions (2008, 2010 and 2013) according to WHO guidelines. Treatment was initially supplied for one month, then provided for three months at a time, with clinical visits scheduled every three months and biological tests performed every six months [5]. In 2005, guidelines recommended treatment for all PLHIV with CD4 ≤ 200 cells/µL, or at WHO stage 3 with CD4 ≤ 350

cells/µL or at WHO stage 4. In 2013, ART was recommended for all PLHIV with CD4 ≤ 500 cells/µL or at WHO stage 3-4 [5].

Definitions

The outcome measures were LTFU, transfer to another care centre or death. LTFU was defined as an interval of at least six months between the last clinical visit and the last database update at each care centre, for PLHIV not known to be dead or to have been transferred elsewhere, because it is the definition yielding the lowest rate of misclassification [8]. As clinicians first consider an individual to be LTFU at the time of the first missed visit, date of LTFU was the date of the last centre visit plus three months [9-10].

Statistical analyses

The follow-up of individuals began with the initiation of ART and was censored at the first of the three competing events (LTFU, transfer or death), after five years on ART or in March 2015, whichever occurred first. We estimated the cumulative incidence of these three events over time and associations of individual characteristics at the start of ART with these events, using univariable and multivariable competing risk regression models [11].

The characteristics of PLHIV recorded at the start of ART were: sex, presence or absence of pregnancy, age, WHO stage and CD4, period of ART initiation, ART regimen, a variable combining the location (Bamako or the regions), expertise level (reference outpatient clinic or hospital) of the care centre and its distance from the individual's home, marital status, level of education and professional activity. The ART initiation periods were selected to coincide with the changes in national guidelines over time. The distance from home to the care centre was determined, in kilometres (km), with Google Maps, by calculating the distance, by road, between the individual's village or quarter of residence and his care centre.

Multiple imputations were performed with chained equations [12] to deal with missing values, assuming data were conditionally missing at random. More specifically, we fitted linear regression, logistic regression and multinomial regression models for CD4 (fourth root), WHO stage, and educational level, respectively. All models

included age, sex, pregnancy, period of ART initiation, region of care and care expertise level, marital status, death and the follow-up time in days (log_{10}) as covariables. We created ten imputed datasets; analyses were run separately on each dataset and the results were combined by Rubin's method [13].

Analyses were conducted with SAS 9.4 (SAS Institute Inc., NC, USA) and STATA 12.1 (STATA Corporation, College Station, TX, USA). The study was approved by the national AIDS programme in Mali in collaboration with the non-governmental organisations ARCAD-SIDA and ESTHER. Written or oral informed consent was obtained from all PLHIV.

Results

Of the 17,730 HIV-positive adults contributing to the ESOPE database and starting ART between 2006 and 2013, 9,821 individuals with CD4 or WHO stage data available at start of ART were included in this study (Supplementary figure 2). Table 1 shows the characteristics of the PLHIV, overall and according to the region of care and the care centre expertise level at the start of ART. Median follow-up time was 29 months [interquartile range (IQR), 10-59]. Individuals with the worst prognostic factors (WHO stage 3-4 and CD4 < 200 cells/µL) were more frequent at regional outpatient clinics (50.7%) and less frequent at Bamako outpatient clinics (22.4%) (Table 1).

Incidence of LTFU, transfer and death

The cumulative incidence of LTFU rose from 15.7% (95% CI: 15.1-16.4) at one year to 35.2% (95% CI: 34.2-36.3) at five years on ART, of transfer to another centre rose from 5.1% (4.7-5.6) at one year to 9.7% (9.1-10.4) at five years, and of mortality rose from 4.0% (3.7-4.4) at one year to 6.7% (6.2-7.2) at five years (Supplementary figure 3).

Risk factors for LTFU and death

Five years after ART initiation, all of the variables studied were associated with LTFU in both univariable and multivariable analyses (Supplementary table 1). Compared to PLHIV followed at Bamako outpatient clinics, risk of being LTFU was approximately 45% higher and three times higher in PLHIV followed at Bamako hospitals if the hospital was located more than 5 km from the individual's home or at the regions hospitals regardless of distance respectively, and 29% higher and 19% lower in people followed at regional outpatient clinics and living less than 5 km from their care centre or living 5-50 km respectively (Figure 1A). Deaths were less frequent at hospitals, whether in Bamako or the regions, than at Bamako outpatient clinics, and more frequent at regional outpatient clinics (Figure 1A).

Figure 1B shows the adjusted risk factors for LTFU by distance from home for each type of care centre. LTFU rates did not differ according to the distance between home and the care centre among the PLHIV followed at

Bamako outpatient clinics. People treated at Bamako hospitals and living 5-50 km or more than 50 km away from their care centre were more likely to be LTFU than those living less than 5 km. For PLHIV treated at regional outpatient clinics, those living 5-50 km or more than 50 km away from their care centres were less likely to be LTFU than those living less than 5 km (Figure 1B).

Discussion

Between 2006 and 2015 in Mali, 15.7% and 35.2% of PLHIV were LTFU within one and five years of starting ART respectively. People followed at Bamako hospitals 5 km or more from their homes, at regional hospitals or at regional outpatient clinics less than 5 km from their homes were at higher risk of LTFU than those followed at Bamako outpatient clinics, whereas people followed at regional outpatient clinics 5-50 km from their homes were at lower risk of LTFU.

Estimated death rates were low, whereas LTFU rates were relatively high. There is no registry of deaths in Mali and the national programme has no dedicated resources for the active tracing of PLHIV [2, 14]. We were therefore unable to estimate the true mortality rate. It is also possible that mortality rates are lower for the more recent periods in which universal ART has been recommended [15]. Moreover, the main objective of the study was to estimate LTFU before death whilst taking deaths among PLHIV remaining in healthcare system into account. Transfers to another care centre were also taken into account as competing risks, to improve the estimation of LTFU and death rates. The main strength of this study is the large number of PLHIV included, corresponding to 64% of those in healthcare in Mali and followed in either the capital or the regions. Without active tracing of people LTFU, Cornell et al [2] observed in South Africa a risk of LTFU of 14.4% (95% CI, 14.1-14.8) and 35.8% (95% CI, 34.3-37.4) at 1 and 5 years respectively, those estimates being close to ours.

Distance from home to care centres is a major obstacle to access to care, and many sub-Saharan countries have tried to decentralise HIV care from hospitals to healthcare centres and other primary health facilities closer to the community [16]. Decentralisation is associated with a shorter travelling distance, higher rates of enrolment in ART programmes and higher levels of retention in healthcare, even if the decrease in distance is only moderate [17]. We also showed that living more than 5 km from the healthcare centre was associated with a higher risk of LTFU for the hospitals, whether in Bamako or the regions, than for Bamako outpatient clinics. Objective measures of transportation are, therefore, required, to optimise PLHIV access to HIV care in resource-limited settings [18].

At outpatient clinics, no difference in LTFU with distance was observed in Bamako, whereas, in the regions, people living less than 5 km from the healthcare centre were more likely to be LTFU than those living more than 5 km away, raising questions about the possibility of HIV-related stigma and secrecy [19]. Better patient-provider communication is associated with a better engagement and re-engagement in HIV, as disrespect, discrimination and scolding are the major reasons for PLHIV disengaging from ART [19].

It is noteworthy that distance was not associated with death in our study as previously reported [20], but death rates were lower in the hospitals than at outpatient clinics, whatever the distance, highlighting the need for improvements in healthcare centre expertise.

We identified several structural risk factors associated with LTFU or death, some of which are modifiable, such as the number and expertise of care centres. Possible stigmatisation for individuals travelling very short distances to the care centres in the regions and insufficient care provision for individuals living at much greater distances should be investigated. ART programmes may increase the success with which PLHIV are retained in the healthcare system, by investing in skills and resources for individual problem-solving rather than offering the standard "education" [19]. A knowledge of the risk factors associated with programme attrition, LTFU or death would help clinicians to identify PLHIV requiring additional support to remain in the healthcare system, and the opening of other healthcare facilities would contribute to the achievement of the UNAIDS targets 90-90-90.

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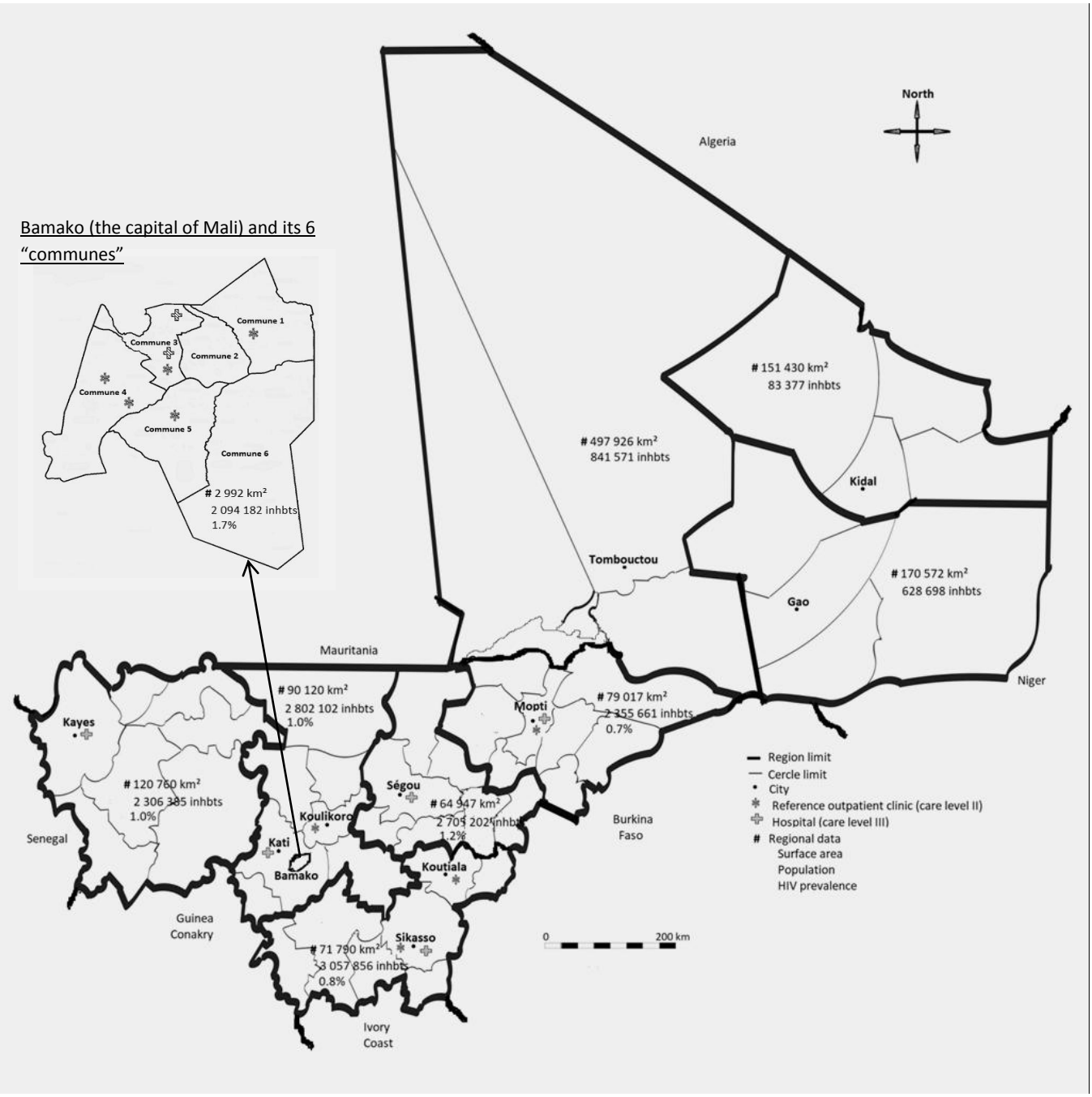
References

1. Ekouevi DK, Balestre E, Ba-Gomis FO, Eholie SP, Maiga M, Amani-Bosse C et al; International epidemiological Database to Evaluate AIDS (IeDEA) West Africa Collaboration. **Low retention of HIV-infected patients on antiretroviral therapy in 11 clinical centres in West Africa.** Trop Med Int Health 2010; 15:34-42.
2. Cornell M, Grimsrud A, Fairall L, Fox MP, van Cutsem G, Giddy J et al; International epidemiological Database to Evaluate AIDS (IeDEA) Southern Africa Collaboration. **Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007**. AIDS 2010; 24:2263–2270.
3. Grimsrud A, Balkan S, Casas EC, Lujan J, Van Cutsem G et al. **Outcomes of antiretroviral therapy over a 10-year period of expansion: a multicohort analysis of African and Asian HIV programs.** JAIDS 2014; 67:e55–e66.
4. Rosen S, Fox MP, Gill CJ. **Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review.** PLoS Med 2007; 4(10):e298.
5. Cellule Sectorielle de Lutte contre le VIH-Sida du Ministère de la Santé et de l'Hygiène Publique (CSLS/MSHP**). Politique et protocoles de prise en charge antirétrovirale du VIH et du Sida**, 2013.
6. Raguin G on behalf of the French ESTHER network. **The ESTHER hospital partnership initiative: a powerful levy for building capacities to combat the HIV pandemic in low-resource countries**. Globalization and Health 2016; 12:12.
7. Cellule Sectorielle de Lutte contre le VIH-Sida du Ministère de la Santé et de l'Hygiène Publique (CSLS/MSHP). **Rapport trimestriel de prise en charge antirétrovirale des personnes vivant avec le VIH**, 1er trimestre 2015.
8. Chi BH, Yiannoutsos CT, Westfall AO, Newman JE, Zhou J, Cesar C et al; International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration. **Universal definition of loss to follow-up in HIV**

treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America. PLoS Med 2011; 8:e1001111.

9. Mberi MN, Kuonza LR, Dube NM, Nattey C, Manda S, Summers R. **Determinants of loss to follow-up in patients on antiretroviral treatment, South Africa, 2004-2012: a cohort study.** BMC Health Serv Res 2015; 15:259.
10. Shepherd BE, Blevins M, Vaz LM, Moon TD, Kipp AM, José E et al. **Impact of definitions of loss to follow-up on estimates of retention, disease progression, and mortality: application to an HIV program in Mozambique.** Am J Epidemiol 2013; 178:819-828.
11. Putter H, Fiocco M, Geskus RB. **Tutorial in biostatistics: competing risks and multistate models**. Statist Med 2007; 26:2389–2430.
12. White IR, Royston P, Wood AM**. Multiple imputation using chained equations: Issues and guidance for practice.** Stat Med 2011; 30: 377–399.
13. Rubin DB. **Multiple imputation for nonresponse in surveys.** New York: Wiley, 1987.
14. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP et al; International epidemiological Database to Evaluate AIDS (IeDEA) East Africa, West Africa and Southern Africa. **Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa**. PLoS Med 2011; 8:e1000390.
15. Geng EH, Odeny TA, Lyamuya RE, Nakiwogga-Muwanga A, Diero L, Bwana M et al. **Estimation of mortality among HIV-infected people on antiretroviral treatment in East Africa: a sampling based approach in an observational, multisite, cohort study.** Lancet HIV 2015; 2:e107-116.
16. Kredo T, Ford N, Adeniyi FB, Garner P. **Decentralising HIV treatment in lower- and middle-income countries.** Cochrane Database Syst Rev 2013; 6:CD009987.

17. Bilinski A, Birru E, Peckarsky M, Herce M, Kalanga N, Neumann C et al. **Distance to care, enrollment and loss to follow-up of HIV patients during decentralization of antiretroviral therapy in Neno District, Malawi: a retrospective cohort study.** PLoS One 2017; 12:e0185699.
18. Siedner MJ, Lankowski A, Tsai AC, Muzoora C, Martin JN, Hunt PW et al. **GPS-measured distance to clinic, but not self-reported transportation factors, are associated with missed HIV clinic visits in rural Uganda.** AIDS 2013; 27:1503-1508.
19. Hurley EA, Harvey SA, Winch PJ, Keita M, Roter DL, Doumbia S et al. **The role of patient-provider communication in engagement and re-engagement in HIV treatment in Bamako, Mali: a qualitative study.** J Health Commun 2018; 23:129-143.
20. Bassett IV, Coleman SM, Giddy J, Bogart LM, Chaisson CE, Ross D et al. **Barriers to care and 1-year mortality among newly diagnosed HIV-infected people in Durban, South Africa.** JAIDS 2017; 74:432-438.



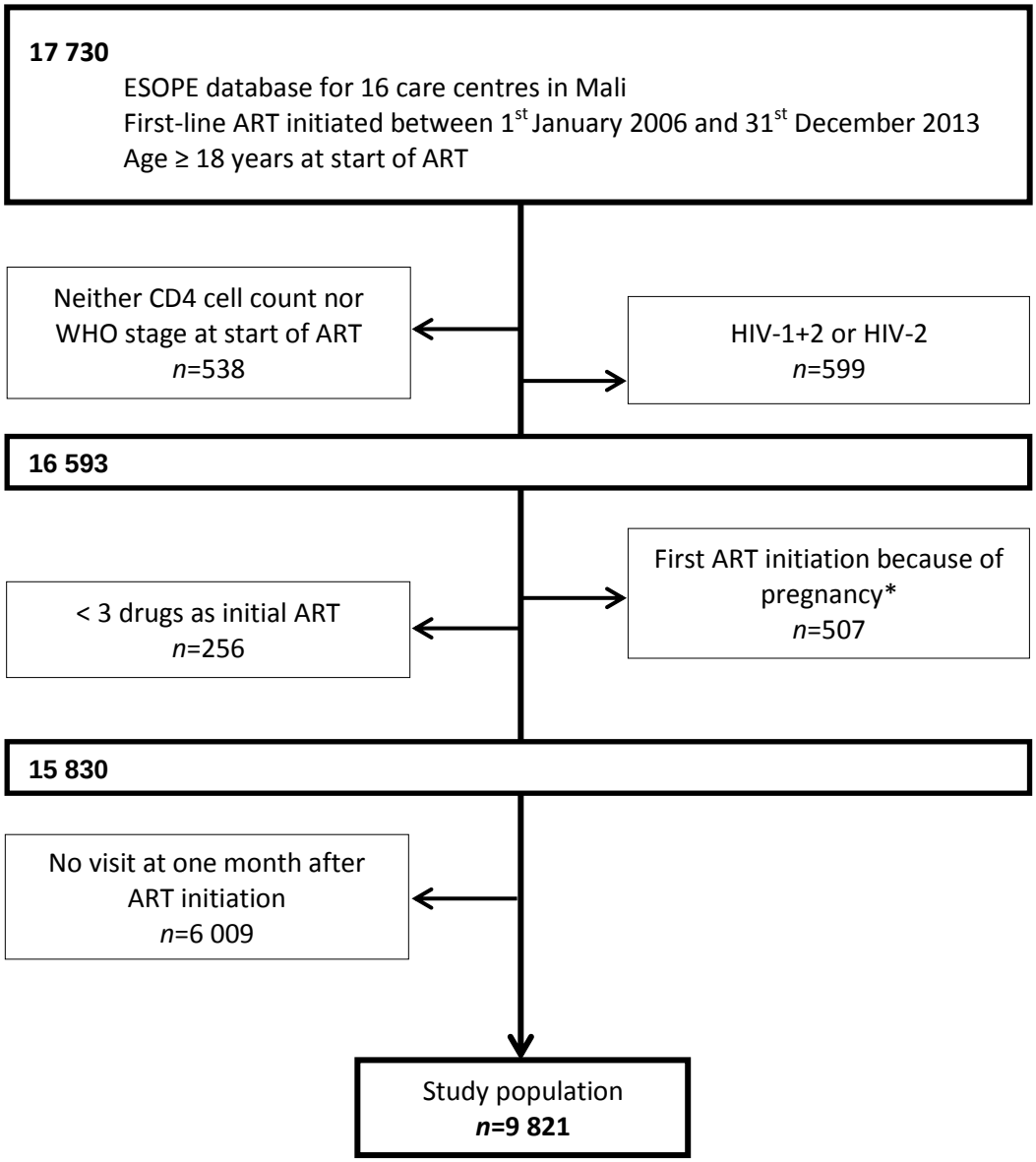
Supplementary figure 1. Map of Mali and its capital (Bamako), showing the location of the study care centres*

Abbreviations: Inhbts, inhabitants; km^2, square kilometres

*Data are from the 2013 national demographic and health survey, except for the three northern regions (Gao, Kidal and Tombouctou), where the survey was not conducted because of the political crisis in 2012 and for which only demographic estimates for 2011 are available.

The communes of Bamako are the administrative boroughs of Bamako; cercles are administrative areas in Mali.

Overall, in Mali, there are 14 (level I), 54 (level II) and 9 (level III) care centres in the regions contributing to the ESOPE database, to which the three regions in northern Mali do not participate (12 additional centres).



Supplementary figure 2. Selection of individuals.

Abbreviations: ART, antiretroviral therapy; WHO, World Health Organisation; PLHIV, people living with HIV.

*****Pregnant women beginning ART at WHO stage 1-2 and/or with a CD4 cell count > 350/µL before 2013 were excluded from this study, because ART initiated for pregnancy was stopped after delivery if clinical stage and biological results at the time of treatment initiation were not within the range of the indication for treatment in the national guidelines for ART.

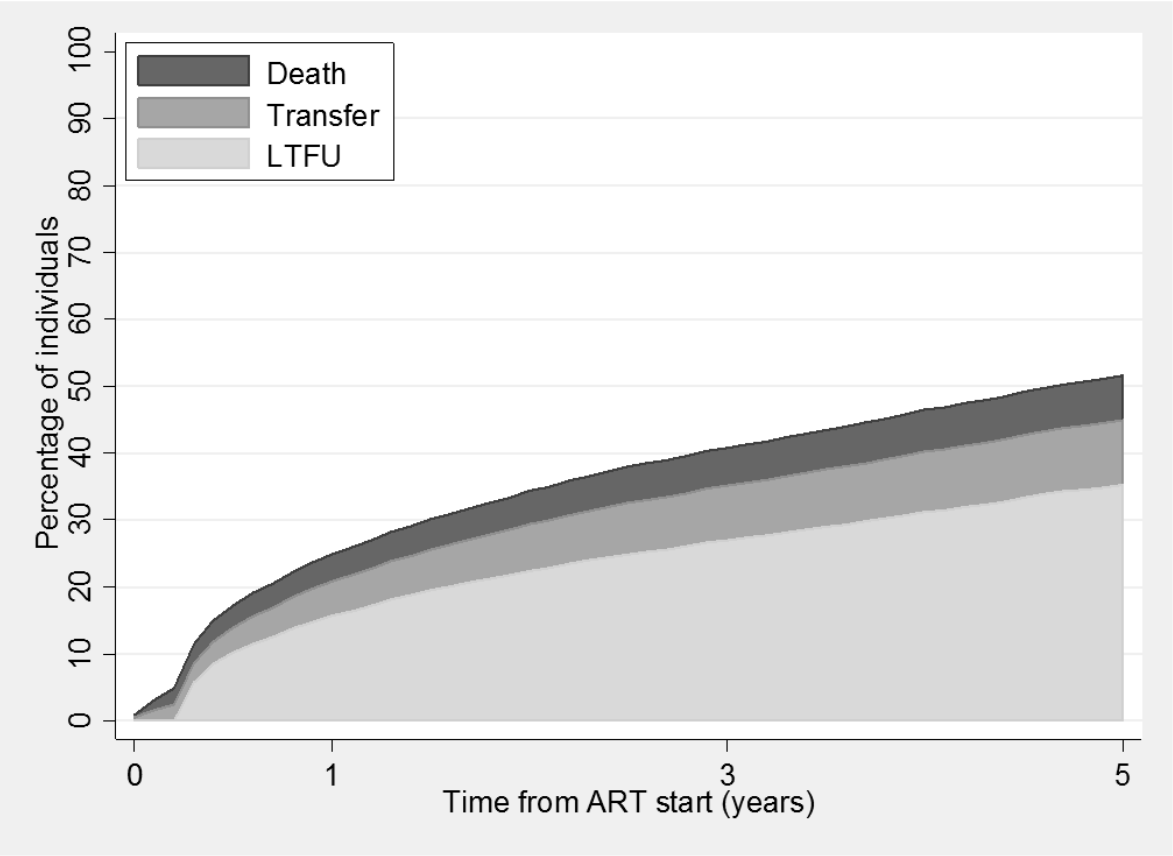
Table 1. Characteristics of individuals, overall and by region and care centre type at the start of antiretroviral therapy (ART)

Characteristics at start of ART	Overall (*n*=9 821)	Bamako outpatient clinics (*n*=5 069)	Bamako hospitals (*n*=2 091)	Regional outpatient clinics (*n*=1 367)	Regional hospitals (*n*=1 294)
Sex and pregnancy					
Men	3 281 (33.4)	1 648 (32.5)	747 (35.7)	426 (31.2)	460 (35.5)
Non-pregnant women	5 734 (58.4)	2 902 (57.3)	1 192 (57.0)	848 (62.0)	792 (61.2)
Pregnant women	806 (8.2)	519 (10.2)	152 (7.3)	93 (6.8)	42 (3.3)
Age (years)	36 (29-43)	35 (29-43)	37 (30-45)	35 (29-43)	36 (30-43)
<30	2 623 (26.7)	1 393 (27.5)	523 (25.0)	371 (27.1)	336 (26.0)
30-40	3 709 (37.8)	1 946 (38.4)	768 (36.7)	505 (37.0)	490 (37.9)
≥40	3 489 (35.5)	1 730 (34.1)	800 (38.3)	491 (35.9)	468 (36.1)
CD4 count cell/µL	153 (56-270)	162 (58-274)	152 (59-271)	146 (55-270)	129 (43-254)
WHO stage and CD4 count cell/µL					
3-4 and CD4<200	3 115 (31.7)	1 137 (22.4)	792 (37.8)	693 (50.7)	493 (38.1)
3-4 and CD4≥200	1 482 (15.1)	532 (10.5)	384 (18.4)	362 (26.5)	204 (15.7)
1-2 and CD4<200	2 830 (28.8)	1 841 (36.3)	480 (23.0)	146 (10.7)	363 (28.0)
1-2 and CD4≥200	2 394 (24.4)	1 559 (30.8)	435 (20.8)	166 (12.1)	234 (18.1)
Periods of ART initiation					
2006-2007	1 997 (20.3)	1 238 (24.4)	354 (16.9)	244 (17.9)	161 (12.5)
2008-2009	1 877 (19.1)	820 (16.2)	480 (23.0)	279 (20.4)	298 (23.0)
2010-2012	4 163 (42.4)	2 056 (40.6)	871 (41.6)	602 (44.0)	634 (49.0)
2013	1 784 (18.2)	955 (18.8)	386 (18.5)	242 (17.7)	201 (15.5)
First NNRTI/PI					
NVP	6 644 (67.7)	3 408 (67.2)	1 276 (61.0)	1 076 (78.7)	884 (68.3)
EFV	2 782 (28.3)	1 428 (28.2)	730 (34.9)	262 (19.2)	362 (28.0)
Other[a]	395 (4.0)	233 (4.6)	85 (4.1)	29 (2.1)	48 (3.7)
First NRTI backbone					
AZT or d4T plus 3TC	7 214 (73.5)	3 499 (69.0)	1 524 (72.9)	1 135 (83.0)	1 056 (81.6)
TDF plus FTC or 3TC	2 330 (23.7)	1 383 (27.3)	498 (23.8)	226 (16.5)	223 (17.2)
Other[b]	277 (2.8)	187 (3.7)	69 (3.3)	6 (0.5)	15 (1.2)
Duration on ART (months)	29 (10-59)	32 (12-64)	31 (14-62)	24 (7-51)	20 (5-45)
Marital status					
Monogamous[c]	4 223 (43.0)	2 162 (42.6)	814 (38.9)	554 (40.5)	693 (53.6)
Polygamous	2 109 (21.5)	1 216 (24.0)	432 (20.7)	317 (23.2)	144 (11.1)
Other[d]	3 489 (35.5)	1 691 (33.4)	845 (40.4)	496 (36.3)	457 (35.3)
Education level					
None	4 543 (46.2)	2 414 (47.6)	659 (31.5)	736 (53.8)	734 (56.7)
Primary/Koranic	2 982 (30.4)	1 493 (29.5)	804 (38.4)	400 (29.3)	285 (22.0)
Secondary	1 707 (17.4)	904 (17.8)	409 (19.6)	195 (14.3)	199 (15.4)
Higher	589 (6.0)	258 (5.1)	219 (10.5)	36 (2.6)	76 (5.9)
Professional activities[e]					
Housewife	3 984 (40.6)	2 154 (42.5)	735 (35.1)	579 (42.3)	516 (39.9)
Public sector staff	594 (6.0)	268 (5.3)	192 (9.2)	46 (3.4)	88 (6.8)
Private sector staff	1 866 (19.0)	1 109 (21.9)	577 (27.6)	90 (6.6)	90 (6.9)
Self-employed	1 588 (16.2)	764 (15.1)	282 (13.5)	349 (25.5)	193 (14.9)
Farmer/Fisherman	605 (6.2)	255 (5.0)	89 (4.3)	124 (9.1)	137 (10.6)
Other	1 184 (12.0)	519 (10.2)	216 (10.3)	179 (13.1)	270 (20.9)
Distance to care centre (km)					
<5	2 412 (24.6)	1 404 (27.7)	350 (16.7)	654 (47.8)	4 (0.3)
5-50	6 269 (63.8)	3 406 (67.2)	1 472 (70.4)	432 (31.6)	959 (74.1)
≥50	1 140 (11.6)	259 (5.1)	269 (12.9)	281 (20.6)	331 (25.6)

Data are counts (proportions) and medians (interquartile range). The percentages of imputed missing data were 15% for CD4 cell count, 8% for WHO stage and 16% for educational level

Abbreviations: SHR, subdistribution hazards ratio; CI, confidence interval; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; EFV, efavirenz; NVP, nevirapine; NRTI, nucleoside reverse transcriptase inhibitor, AZT, zidovudine; d4T, stavudine; 3TC, lamivudine; TDF, tenofovir; FTC, emtricitabine.

[a]Others: PI (lopinavir/ritonavir, indinavir/ritonavir, saquinavir/ritonavir and atazanavir/ritonavir) or NRTIs in 3-NRTI combinations. [b]Others NRTI: abacavir (ABC)/didanosine (ddI), ABC/3TC, ddI/3TC, TDF/ddI and TDF/ABC. [c]Married or living with a partner. [d]Other for marital status: single, divorced, widowed and missing (6%). [e]Professional activities: professional activity categories combined types and sectors of employment, housewife without any professional activity, public or private sector salaried employment, various non-salaried activities, such as being self-employed, farmer/fisherman and other (unemployed and missing (3%)).



	N			
LTFU	3 090	15.7 (15.1-16.4)	27.0 (26.2-27.8)	35.2 (34.2-36.3)
Transfer	872	5.1 (4.7-5.6)	8.1 (7.6-8.7)	9.7 (9.1-10.4)
Death	607	4.0 (3.7-4.4)	5.7 (5.2-6.2)	6.7 (6.2-7.2)

Supplementary figure 3. Stacked cumulative incidence functions of loss to follow-up (LTFU), transfer and death, estimated with competing risks methods. The figures below the graph are the estimated cumulative incidence of each event at 1, 3 and 5 years, with 95% confidence intervals (CIs).

Abbreviations: LTFU, loss to follow-up; ART, antiretroviral therapy

Supplementary table 1. Competing risks regression analysis of associations of individual characteristics with LTFU, transfer or death

	Total (*N*=9 821)	LTFU (*N*=3 090)			Transfer (*N*=872)		Death (*N*=607)	
			Univariable	Multivariable		Multivariable		Multivariable
	n	*n*	SHR (95% CI) *p*-value	SHR (95% CI) *p*-value	*n*	SHR (95% CI) *p*-value	*n*	SHR (95% CI) *p*-value
Sex and pregnancy			**<0.0001**	**<0.0001**		**0.0007**		**0.0001**
Men	3 082	1 091	1	1	253	1	253	1
Non-pregnant women	5 431	1 864	0.97 (0.90-1.04)	0.86 (0.78-0.96)	579	1.18 (0.96-1.44)	335	0.80 (0.64-0.99)
Pregnant women	794	135	0.42 (0.35-0.50)	0.46 (0.38-0.55)	40	0.52 (0.36-0.76)	19	0.30 (0.18-0.49)
Age (years)			**0.9364**	**0.0009**		**0.0127**		**0.2008**
<30	2 507	835	1	1	241	1	156	1
30-40	3 509	1 173	0.99 (0.91-1.08)	0.93 (0.85-1.01)	349	0.99 (0.84-1.18)	219	0.87 (0.71-1.08)
≥40	3 291	1 082	0.98 (0.90-1.08)	0.85 (0.77-0.93)	282	0.79 (0.66-0.95)	232	0.88 (0.71-1.09)
WHO stage and CD4 count cell/µL			**<0.0001**	**0.0111**		**0.0781**		**<0.0001**
3-4 and CD4<200	3 115	1 098	1	1	316	1	323	1
3-4 and CD4≥200	1 482	472	0.86 (0.77-0.97)	0.93 (0.83-1.04)	167	1.07 (0.87-1.31)	98	0.65 (0.50-0.83)
1-2 and CD4<200	2 830	870	0.86 (0.79-0.95)	0.98 (0.89-1.08)	202	0.81 (0.67-0.99)	129	0.44 (0.35-0.57)
1-2 and CD4≥200	2 394	650	0.74 (0.67-0.82)	0.87 (0.79-0.97)	187	0.84 (0.69-1.02)	57	0.24 (0.18-0.33)
Periods of ART initiation			**<0.0001**	**<0.0001**		**<0.0001**		**0.0001**
2006-2007	1 997	504	1	1	115	1	149	1
2008-2009	1 877	415	0.81 (0.72-0.93)	0.75 (0.66-0.85)	178	1.74 (1.38-2.21)	119	0.76 (0.59-0.97)
2010-2012	4 163	1 529	1.80 (1.62-2.00)	1.71 (1.53-1.91)	460	2.23 (1.80-2.77)	266	0.72 (0.57-0.90)
2013	1 784	642	2.62 (2.32-2.97)	2.71 (2.37-3.10)	119	1.52 (1.15-2.01)	73	0.50 (0.37-0.68)
First NNRTI/PI			**0.0005**	**0.0008**		**0.2856**		**0.0366**
NVP	6 644	2 069	1	1	593	1	426	1
EFV	2 782	892	1.17 (1.08-1.26)	0.85 (0.77-0.93)	253	1.08 (0.90-1.29)	149	0.75 (0.59-0.95)
Other[a]	395	129	1.07 (0.89-1.28)	1.16 (0.97-1.38)	26	0.81 (0.54-1.20)	32	1.25 (0.87-1.79)
First NRTI backbone			**<0.0001**	**0.0035**		**0.5942**		**0.0001**
AZT or d4T plus 3TC	7 214	2 197	1	1	634	1	439	1
TDF plus FTC or 3TC	2 330	791	1.38 (1.28-1.50)	1.13 (1.02-1.26)	213	0.92 (0.76-1.13)	150	1.65 (1.29-2.11)
Other[b]	277	102	1.45 (1.19-1.77)	1.33 (1.09-1.62)	25	0.89 (0.59-1.35)	18	1.51 (0.91-2.49)
Marital status			**<0.0001**	**0.0551**		**0.0004**		**0.5043**
Monogamous[c]	4 223	1 386	1	1	332	1	265	1
Polygamous	2 109	569	0.80 (0.73-0.88)	0.91 (0.82-0.99)	247	1.40 (1.18-1.66)	139	1.08 (0.87-1.33)
Other[d]	3 489	1 135	0.99 (0.91-1.07)	1.05 (0.97-1.14)	293	1.05 (0.90-1.24)	203	0.96 (0.80-1.16)
Educational level			**0.0003**	**0.0014**		**0.2237**		**0.3958**
None	4 543	1 550	1	1	479	1	293	1
Primary/Koranic	2 982	876	0.84 (0.76-0.92)	0.89 (0.81-0.98)	240	0.90 (0.76-1.07)	185	1.02 (0.84-1.24)
Secondary	1 707	487	0.81 (0.72-0.91)	0.83 (0.73-0.94)	116	0.85 (0.66-1.08)	89	0.89 (0.67-1.17)
Higher	589	177	0.85 (0.71-1.03)	0.82 (0.67-1.00)	37	1.00 (0.67-1.49)	40	1.34 (0.92-1.95)
Professional activities[e]			**<0.0001**	**0.0128**		**0.0001**		**0.3255**
Housewife	3 984	1 265	1	1	421	1	211	1
Public sector staff	594	169	0.86 (0.73-1.00)	0.86 (0.72-1.02)	25	0.52 (0.33-0.82)	40	1.36 (0.91-2.04)
Private sector staff	1 866	490	0.81 (0.73-0.90)	0.86 (0.76-0.97)	101	0.60 (0.47-0.77)	100	1.16 (0.87-1.55)
Self-employed	1 588	493	0.98 (0.88-1.08)	0.90 (0.80-1.01)	145	0.93 (0.75-1.16)	134	1.25 (0.97-1.61)
Farmer/Fisherman	605	252	1.42 (1.24-1.63)	1.15 (1.00-1.33)	90	1.53 (1.14-2.05)	47	1.05 (0.72-1.53)
Other	1 184	421	1.12 (1.00-1.25)	1.03 (0.91-1.16)	90	0.90 (0.70-1.15)	75	1.10 (0.81-1.48)
Regions, care centre & distance (km)			**<0.0001**	**<0.0001**		**<0.0001**		**<0.0001**
Bamako outpatient clinics	5 069	1 233	1	1	459	1	296	1
Bamako hospitals & <5	350	86	0.98 (0.80-1.22)	1.05 (0.85-1.30)	21	0.66 (0.43-1.02)	10	0.39 (0.21-0.74)
Bamako hospitals & 5-50	1 472	475	1.39 (1.25-1.55)	1.51 (1.35-1.68)	84	0.61 (0.48-0.78)	35	0.32 (0.22-0.46)
Bamako hospitals & ≥50	269	88	1.45 (1.17-1.81)	1.42 (1.14-1.77)	22	0.76 (0.49-1.18)	8	0.37 (0.18-0.76)
Regional outpatient clinics & <5	654	206	1.23 (1.07-1.42)	1.29 (1.11-1.50)	82	1.17 (0.91-1.50)	108	2.04 (1.59-2.61)
Regional outpatient clinics & 5-50	432	103	1.04 (0.85-1.27)	0.81 (0.66-0.99)	40	0.76 (0.54-1.06)	58	1.87 (1.39-2.50)
Regional outpatient clinics & ≥50	281	68	0.97 (0.76-1.23)	0.92 (0.72-1.18)	67	2.05 (1.56-2.70)	36	1.68 (1.16-2.43)
Regional hospitals & <50	963	616	3.09 (2.82-3.38)	3.03 (2.76-3.33)	57	0.52 (0.39-0.69)	44	0.65 (0.47-0.90)
Regional hospitals & ≥50	331	215	3.28 (2.86-3.75)	3.06 (2.67-3.51)	40	1.00 (0.71-1.39)	12	0.50 (0.28-0.90)

Abbreviations: SHR, subdistribution hazards ratio; CI, confidence interval; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; EFV, efavirenz; NVP, nevirapine; NRTI, nucleoside reverse transcriptase inhibitor, AZT, zidovudine; d4T, stavudine; 3TC, lamivudine; TDF, tenofovir; FTC, emtricitabine.

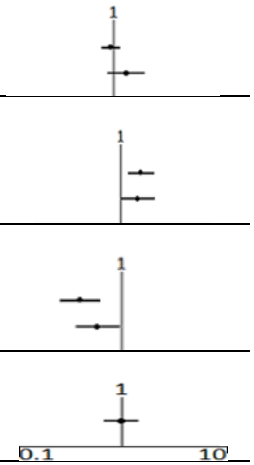
[a]Other: PI (lopinavir/ritonavir, indinavir/ritonavir, saquinavir/ritonavir and atazanavir/ritonavir) or NRTIs in 3-NRTI combination. [b]Other NRTI: abacavir (ABC)/didanosine (ddI), ABC/3TC, ddI/3TC, TDF/ddI and TDF/ABC. [c]Married or living with a partner. [d]Other marital status: single, divorced, widowed and missing (6%). [e]Professional activities: professional activity categories combined types and sectors of employment, housewife without any professional activity, public or private sector salaried employment, various non-salaried activities, such as being self-employed, farmer/fisherman and other (unemployed and missing (3%)).

A

Regions, care centre & distance (km)*	Total (*N*=9 821) *n*	LTFU (*N*=3 090) *n*	LTFU (*N*=3 090) Multivariable SHR (95% CI)	Transfer (*N*=872) *n*	Transfer (*N*=872) Multivariable SHR (95% CI)	Death (*N*=607) *n*	Death (*N*=607) Multivariable SHR (95% CI)
Bamako outpatient clinics	5 069	1 233	1	459	1	296	1
Bamako hospitals & <5	350	86	1.05 (0.85-1.30)	21	0.66 (0.43-1.02)	10	0.39 (0.21-0.74)
Bamako hospitals & 5-50	1 472	475	1.51 (1.35-1.68)	84	0.61 (0.48-0.78)	35	0.32 (0.22-0.46)
Bamako hospitals & ≥50	269	88	1.42 (1.14-1.77)	22	0.76 (0.49-1.18)	8	0.37 (0.18-0.76)
Regional outpatient clinics & <5	654	206	1.29 (1.11-1.50)	82	1.17 (0.91-1.50)	108	2.04 (1.59-2.61)
Regional outpatient clinics & 5-50	432	103	0.81 (0.66-0.99)	40	0.76 (0.54-1.06)	58	1.87 (1.39-2.50)
Regional outpatient clinics & ≥50	281	68	0.92 (0.72-1.18)	67	2.05 (1.56-2.70)	36	1.68 (1.16-2.43)
Regional hospitals & <50	963	616	3.03 (2.76-3.33)	57	0.52 (0.39-0.69)	44	0.65 (0.47-0.90)
Regional hospitals & ≥50	331	215	3.06 (2.67-3.51)	40	1.00 (0.71-1.39)	12	0.50 (0.28-0.90)

B

Distance from home (km)*	*N*	LTFU Multivariable *n*	LTFU Multivariable SHR (95% CI)
Bamako outpatient clinics (*N*=5 069)			
<5	1 404	357	1
5-50	3 406	804	0.95 (0.84-1.08)
≥50	259	72	1.18 (0.91-1.52)
Bamako hospitals (*N*=2 091)			
<5	350	86	1
5-50	1 472	475	1.41 (1.13-1.78)
≥50	269	88	1.34 (1.00-1.81)
Regional outpatient clinics (*N*=1 367)			
<5	654	206	1
5-50	432	103	0.58 (0.44-0.75)
≥50	281	68	0.72 (0.54-0.97)
Regional hospitals (*N*=1 294)			
<50	963	616	1
≥50	331	215	1.00 (0.84-1.16)



Abbreviations. LTFU, loss to follow-up; SHR, subdistribution hazards ratio; CI, confidence interval.

Figure 1. A) Adjusted subdistribution hazard ratios (SHRs) for loss to follow-up (LTFU), transfer to another centre and death according to a variable combining regions of care, care expertise level and distance (km) from home and **B)** Adjusted SHRs for LTFU taking into account transfer to another centre and death as competing risk events, for each type of care centre according to distance (km) from home (Cox model).

*SHR adjusted for variables at the start of ART: sex and pregnancy, age, WHO stage and CD4 count, period of ART initiation, initial ART regimen, marital status, educational level and professional activities.