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Use of pre-ART laboratory screening to identify renal, hepatic, and hematological abnormalities in Côte d'Ivoire

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Abstract

Background: High demand for HIV-services and extensive clinical guidelines force health systems in low-resource settings to dedicate resources to service delivery at the expense of other priorities. Simplifying services may reduce the burden on health systems and pre-antiretroviral therapy (ART) laboratory screening is among the services under consideration for simplification.

Methods: We assessed the frequencies of conditions linked to ART toxicities among 34,994 adult, ART-naïve patients with specimens referred to the RETRO-CI laboratory in Abidjan, Côte d'Ivoire between 1998 and 2017. Screening included tests for serum creatinine, alanine aminotransferase (ALT), and hemoglobin (Hb) to identify renal dysfunction (estimated glomerular filtration rate<50 mL/min), hepatic abnormalities (ALT >5x upper limit of normal), and severe anemia (Hb <6.5 g/dL), respectively. We considered screening results across four eras and identified factors associated with the conditions in question.

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Ethics

The protocol for this study was reviewed and approved by the Ivorian Ethics Review Committee (*Comité National d'Éthique des Sciences de la Vie et de la Santé*) and the Office of the Associate Director for Science of the U.S. Centers for Disease Control and Prevention (CDC).

Results: The prevalence of renal dysfunction, hepatic abnormalities, and severe anemia were largely unchanged over time and just 8.4% of patients had any of the three conditions. Key factors associated with renal dysfunction and severe anemia were age >50 years (adjusted odds ratio (aOR): 2.53; 95% confidence interval (CI): 2.19–2.92; $p<0.001$) and CD4 <100 cells/μl (aOR: 2.57; 95% CI: 2.30–2.88; $p<0.001$), respectively.

Conclusion: The relative infrequency of conditions linked to toxicity in Côte d'Ivoire supports the notion that simplification of pre-ART laboratory screening may be undertaken with limited negative impact on identification of adverse events. Targeted screening may be a feasible strategy to balance detection of conditions associated with ART toxicities with simplification of services.

Keywords

HIV; toxicity; Côte d'Ivoire; anemia

Introduction

Over the last decade, evidence favoring earlier initiation of antiretroviral therapy (ART) led to a series of recommendations by the World Health Organization (WHO) that aimed to put people living with HIV (PLHIV) on treatment at higher CD4 count thresholds, culminating in 2016 with the recommendation to 'treat all' PLHIV with ART regardless of CD4 count (1–4). This, in combination with ongoing and evolving efforts to identify new PLHIV and link them to care, has significantly increased demand for HIV services and appears likely to continue doing so for years to come. In many sub-Saharan African settings, the combination of high demand for services and limited funding availability forces programs to dedicate resources to service delivery at the expense of other priorities. Efforts are underway to address this issue through implementation of differentiated service delivery models that incorporate approaches such as task shifting and simplification of services (5). Notably, pre-ART laboratory screening, which is recommended in many low-resource settings (6), is among the services being considered for simplification (7).

Specimens for pre-ART laboratory screening are typically drawn during a clinic visit following HIV diagnosis and either tested at a hospital laboratory or transported to a central laboratory for testing. The menu of tests varies by setting, but almost always includes serum creatinine, used to calculate estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), and hemoglobin (Hb); which assist in the identification of renal dysfunction (low eGFR), hepatic abnormalities (elevated ALT), and severe anemia (low Hb), respectively. Following screening, results are returned to the clinic where they are used to inform patient management plans and identify patients at risk for ART toxicities. Patients with anemia, for example, may be recommended for enhanced patient monitoring. Similarly, modified ART regimens may be prescribed for patients with renal dysfunction, which is linked to tenofovir) toxicity (8); hepatic abnormalities, which are associated with nevirapine toxicity (4); or severe anemia, which may be exacerbated by zidovudine (9–11).

While the considerable effort required to provide pre-ART laboratory screening to PLHIV may have been warranted in the past, current circumstances suggest the time is ripe to simplify this service. In addition to the challenges posed by increasing demand for HIV

services, ART regimens are less-toxic than they were previously (12), WHO has endorsed symptom-directed toxicity monitoring (4), and rapid ART initiation models that incorporate simplified versions of pre-ART screening have been shown to be both safe and effective (13–15). However, the absence of longitudinal data showing the prevalence of specific toxicities related to ART regimens are a barrier to simplification in many settings, where region or country-specific evidence is needed to justify modifications to existing standards of care. Given this, we assessed the frequency of low eGFR, elevated ALT, and severe anemia identified by pre-ART laboratory screening in Côte d'Ivoire.

Methods

Setting

This retrospective study assessed pre-ART laboratory screening results from patient specimens referred to the RETRO-CI laboratory in Abidjan, Côte d'Ivoire. All specimens were referred to the laboratory and tested between 1998 and 2017. Clinics referring specimens to the RETRO-CI laboratory varied throughout the years, peaking at 7 in 2005 prior to decentralization of HIV-related laboratory testing in Côte d'Ivoire. Between 2005 and 2017 just two clinics in Abidjan referred specimens to the RETRO-CI laboratory. Project RETRO-CI is a collaboration between the U.S Centers for Disease Control and Prevention (CDC) and the Ivorian Ministry of Health that provides laboratory testing and data management support to the clinics referring patient specimens to the RETRO-CI laboratory. Data for this study were extracted from the RETRO-CI database.

Inclusion criteria

Only specimens referred from adult (≥15 years), ART-naïve patients were included in the study. If patients had multiple pre-ART specimens referred to the RETRO-CI laboratory, only the screening results from the specimen collected immediately prior to ART initiation were included.

Baseline screening and definitions of abnormalities

Laboratory screening was conducted on all specimens referred to the RETRO-CI laboratory (16). Screening included a full blood count, CD4 cell count, serum creatinine, and a liver enzyme test (alanine aminotransferase (ALT)). Serum creatinine was used to estimate glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (17). Low eGFR was defined as eGFR <50 ml/min per WHO guidelines (4). Elevated ALT was defined as >5 times the upper limit of normal range, with normal ALT range defined by the laboratory. For RETRO-CI, the upper limit of normal was 26 IU/L for males and 24 IU/L for females. Anemia was defined as Hb <12 g/dL (for males) and Hb <11 g/dL (for females); severe anemia was defined as Hb <6.5 g/dL to reflect the definition of severe anemia used in WHO's ART guidelines (4).

Data Analysis

Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC). The dataset utilized may be requested from the RETRO-CI laboratory and the Ivorian Ministry of Health.

Screening results were considered in four eras roughly defined by timing of updates to the WHO guidelines for treating and preventing HIV infections: 1998 – 2005 (1), 2006 – 2010 (2), 2011 – 2014 (3), 2015 – 2017 (4). Two sample t-tests were used to compare normally distributed variables across eras, while Mann-Whitney tests were similarly used to make nonparametric comparisons. Chi-square tests were used to compare categorical variables. The prevalence of having one or more condition (low eGFR, elevated ALT, severe anemia) was compared across eras and logistic regression was used to model the relationships between the outcomes of low eGFR, elevated ALT, severe anemia status, and the binary variables of age ≤50 years or >50 years, CD4 <100 cells/μl or ≥100 cells/μl, and gender (which was a binary variable in the dataset utilized for this analysis). Multiple variable regression models were adjusted for HIV-type, era, age, CD4 count, and gender.

Results

Results of pre-ART laboratory screening for 34,994 adult, ART-naïve patients are summarized in Table 1. Overall, nearly 60% of patients were female and 92.8% were infected with HIV-1 (vs. HIV-2 or HIV-D). During the earliest era (1998—2005) nearly 38% (9,189) of patients had pre-ART CD4 counts <100 cells/μl, which decreased to approximately 31% (496) in the most recent era (2015—2017). Similarly, anemia was common during the earliest era (72.2%), but was identified at a significantly lower prevalence in the most recent era (55.2%). The frequencies of low eGFR, elevated ALT, and severe anemia did not differ significantly across eras. Overall, 8.4% (2,949) of patients were identified as having any of the three conditions associated with ART toxicities.

Factors associated with renal dysfunction, elevated ALT, and severe anemia are summarized in Figure 1. CD4 <100 cells/μl was a significant positive predictor for both low eGFR and severe anemia, and a negative predictor for elevated ALT. Age >50 years and female sex were also significant positive predictors for low eGFR and severe anemia, respectively.

Discussion

Results indicated that prevalence of ART-naïve adult PLHIV in Côte d'Ivoire presenting with low eGFR, elevated ALT, or severe anemia was low, largely unchanged between 1998 and 2017, and independently predicted by factors such as female sex, CD4 count <100 cells/μl and age >50 years. Even though patients at risk for ART toxicities is a concern, the relative infrequency of these conditions in Côte d'Ivoire supports the notion that simplification of pre-ART laboratory screening may be undertaken with limited negative impact on identifying patients at risk for adverse events.

Targeted pre-ART screening may be a feasible strategy to balance detection of conditions associated with ART toxicities with simplification of services. By limiting pre-ART screening to patients at the greatest risk for conditions linked to ART toxicities (based on predictive factors), targeted screening both serves the most vulnerable patients and reduces demand for HIV services. To provide an example of the potential implications of this strategy we estimated the number of baseline screening tests that the RETRO-CI laboratory would have needed to conduct in order to identify 50 patients with abnormal

kidney function under a targeted screening strategy in which just those patients >50 years of age received baseline screening tests. Based on data from the the two most recent eras, it would have required approximately 614 tests to find 50 patients with abnormal kidney function using targeted baseline screening (versus 1,555 tests needed under a non-targeted baseline screening strategy). Similarly, targeted screening for only those with CD4 <100 cells/μl would have necessitated screening for just 910 patients to identify 50 with severe anemia (versus 2,359 tests needed under a non-targeted screening strategy). Importantly, in addition to the potential implications for commodities and human resources that a targeted screening strategy might yield, such an approach could also be incorporated into screening algorithims for other diseases. One potential example is the incorporation of screening for anemia into tuberculosis (TB) screening algorithims, as reports indicate that anemia is a associated with both tuberculosis (TB) and poorer TB outcomes (18, 19).

It is notable that our findings largely concur with studies conducted elsewhere in sub-Saharan Africa, suggesting that there is a strong case for simplification of pre-ART laboratory screening beyond Côte d'Ivoire. The frequencies of elevated ALT, severe anemia, and low eGFR among adult PLHIV found in Côte d'Ivoire were comparable to rates reported across the continent, including South Africa (7) and Tanzania (20) (for elevated ALT), Uganda (11, 21) and Zambia (22) (for severe anemia), and seven sub-Saharan African countries (23) (for low eGFR). Similarly, factors we identified as positive predictors for low eGFR and severe anemia in Côte d'Ivoire, have been reported previously in sub-Saharan Africa (23, 24).

Targeted pre-ART laboratory screening faces logistical challenges brought about by the success of trials examining rapid and same-day ART initiation (13–15). That is, how can targeted pre-ART laboratory screening results be generated quickly enough to inform treatment decisions, but not compromise the benefits associated with faster ART initiation? While targeted screening reduces the number of patients requiring screening, the time required to collect, transport, and test specimens may delay current models of rapid or same-day ART initiation. Point-of-care (POC) technology is a potential solution to this challenge and POC tests for CD4, serum creatinine, ALT and hemoglobin have been used effectively in studies examining rapid (13) and same-day (15) ART initiation. However, there are barriers to the adoption and wide-scale implementation of POC testing platforms; including policy, infrastructure, cost, quality assurance, and supply chain (25). An additional challenge for targeted pre-ART laboratory screening is the recent deprioritization of pre-ART CD4 testing by large donor orgainzations. If pre-ART CD4 testing were to be identified as a critical component of targeted pre-ART laboratory screening there would need to be a coordinated effort to address its continued funding. The logistics surrounding universal pre-ART CD4 testing would also need to be addressed, with POC technology serving as a potential solution. Alternatively, criteria such as WHO clinical staging could be used to inform pre-ART baseline screening where CD4 testing is not feasible.

Key strengths of this study are the large, well-characterized population and the availability of data dating back to 1998. There were also several limitations. First, the study considered patients with low eGFR, elevated ALT, and severe anemia to be at risk for ART toxicities regardless of the ART regimens in use at the time or that were ultimately prescribed. Second,

the variables available for examination were restricted to those included in the RETRO-CI laboratory database, thus we were unable to adjust for additional conditions such as viral hepatitis, alcohol use, low body weight, pre-existing renal disease, untreated hypertension or diabetes and other conditions which could have predisposed or contributed to low eGFR, elevated ALT and severe anemia. Finally, the dataset analyzed for this study represents a fraction of PLHIV in Côte d'Ivoire (particularly from 2005 – 2017) and may not be representative of the larger population.

Conclusion

Pre-ART laboratory screening in Côte d'Ivoire between 1998 and 2017 identified a relatively small number of patients at risk for ART toxicities or in need of specific patient-management plans based on screening results. Further analyses indicated that those patients were more likely to be female, older than 50 years, or have CD4 <100 cells/μl. While a strategy such as targeted pre-ART screening may both balance the need to simplify this service and identify patients at risk for adverse events, additional research into its feasibility is needed especially within the context of same day or rapid ART initiation.

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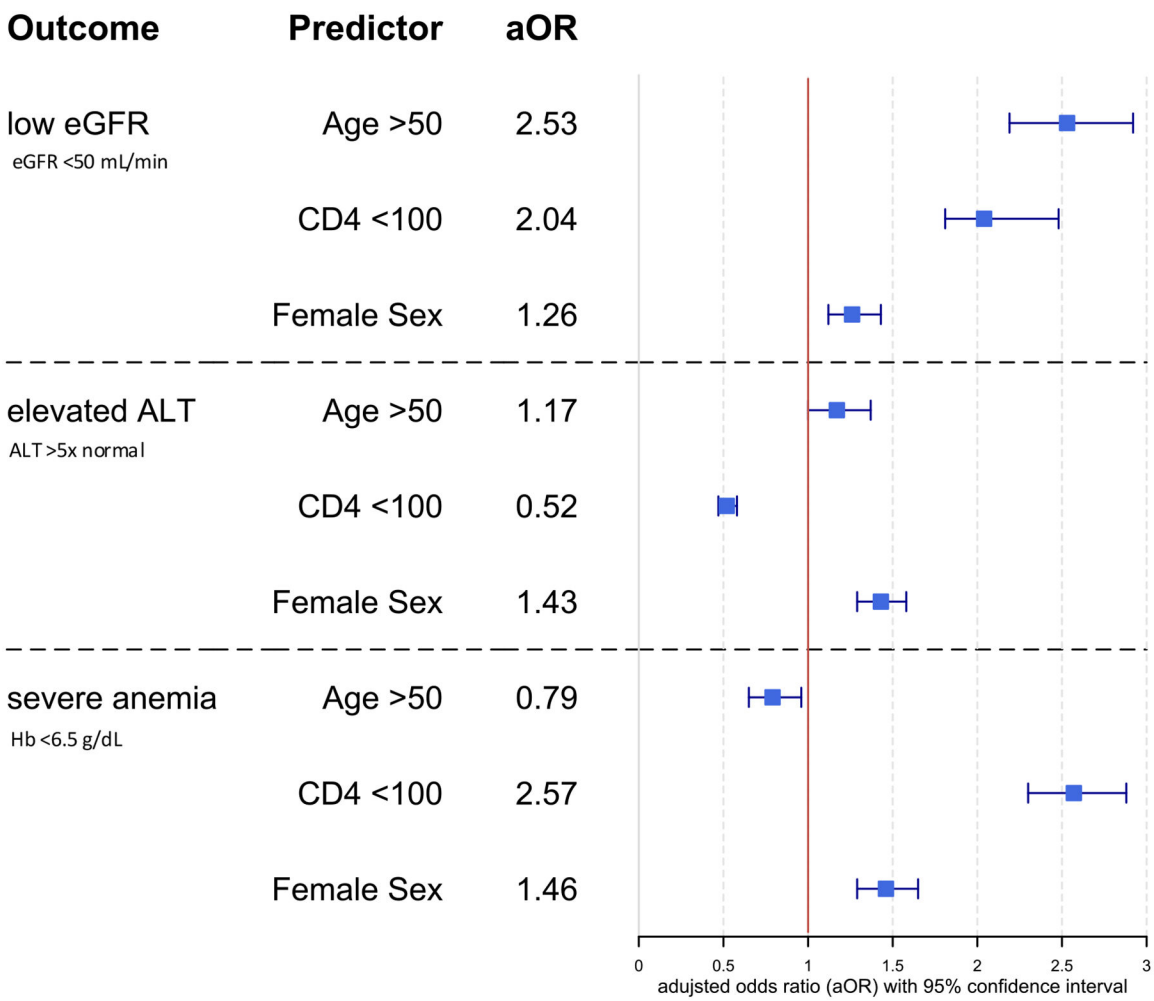

Figure 1. Predictors of renal, hepatic, and hematological abnormalities among adult PLHIV in Côte d'Ivoire, 1998—2017.

Factors associated with low eGFR, elevated ALT, and severe anemia at pre-ART laboratory screening for 35,994 adult PLHIV in Côte d'Ivoire. Three multiple variable logistic regression models were utilized to assess the relationship between low eGFR, elevated ALT, and severe anemia and three independent variables (age >50, CD4<100, and female sex). All models were adjusted for age, sex, CD4 count, era, and HIV type.

aOR, adjusted odds ratio; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase: Hb, hemoglobin

Table 1.

Clinical characteristics for HIV+, ART-naïve adults (≥15 years) referred to the RETRO-C laboratory for laboratory baseline screening, 1998 – June 30, 2017

	1998–2005	2006–2010	2011–2014	2015–2017
N[a,b,c]	24281	7298	1800	1615
Female	14388, 59.3%	4501, 61.7%	1110, 61.7%	945, 58.5%
HIV-1	21986, 92.5%	6635, 93.8%	1323, 91.4%	508, 92.7%
HIV-2	817, 3.4%	273, 3.9%	59, 4.1%	30, 5.5%
HIV-1/2	955, 4.0%	167, 2.4%	65, 4.5%	10, 1.8%
Age, years	38 ±11.8	38 ±10.3	40 ±10.5	41 ±10.6[d]
Female	35 ±11.4	36 ±10.1	38 ±10.3	39 ±10.5[d]
Male	41 ±11.3	42 ±9.3	44 ±9.9	45 ±9.9[d]
CD4 count <100 cells/μl	9189, 37.8%	2353, 32.2%	560, 31.1%	496, 30.7%[f]
Female	4908, 34.1%	1276, 28.4%	312, 28.1%	259, 27.4%[f]
Male	4281, 43.4%	1077, 38.5%	248, 35.9%	237, 35.4%[f]
Anemia	17521, 72.2%	4572, 62.7%	1150, 63.9%	892, 55.2%[f]
Female	10542, 73.3%	2799, 62.2%	690, 62.2%	500, 52.9%[f]
Male	6979, 70.5%	1773, 63.4%	460, 66.7%	392, 58.5%
Severe Anemia	996, 4.1%	286, 3.9%	69, 3.8%	46, 2.9%
Female	648, 4.5%	194, 4.3%	48, 4.3%	25, 2.7%
Male	348, 3.5%	92, 3.3%	21, 3.0%	21, 3.1%
AST 2.5x – 5x normal	2102, 8.7%	614, 8.6%	142, 12.2%	101, 7.6%
AST >5x normal	688, 2.9%	190, 2.7%	56, 3.2%	35, 2.6%
ALT 2.5x – 5x normal	1353, 5.6%	349, 4.9%	94, 5.5%	78, 5.8%
ALT >5x normal	398, 1.7%	89, 1.3%	28, 1.6%	31, 2.3%
Abnormal eGFR	839, 3.5%	276, 3.9%	72, 4.1%	59, 4.0%
Abnormal eGFR and/or severe anemia	1686, 6.9%	529, 7.3%	127, 7.1%	98, 6.1%
Abnormal eGFR and/or severe anemia and/or ALT >5x normal	2052, 8.5%	616, 8.4%	154, 8.6%	127, 7.9%

Values are reported as mean ±SD, or n, %. Anemia: hemoglobin level <12 g/dL for males, <11 g/dL for females. Severe anemia: hemoglobin level <6.5 g/dL. High end of normal range for AST: 32 UI/L (male), 30 UI/L (female). High end of normal range for ALT: 26 UI/L (male), 24 UI/L (female). eGFR calculated using CKD-EPI Creatinine Equation. Abnormal eGFR: <50 ml/min.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate

[a] N for HIV-type: 1998–2005: 23758, 2006–2010: 7075; 2011–2014: 1447; 2015–2017: 548

[b] N for AST/ALT: 1998–2005: 24097, 2006–2010: 7108; 2011–2014: 1725; 2015–2017: 1339

[c] N for eGFR: 1998–2005: 23874, 2006–2010: 7005; 2011–2014: 1762; 2015–2017: 1466

[d] Values were significantly greater in the 2015–2017 era compared to all other eras combined (two sample t-test; $p<0.001$)

[e] Values were significantly greater in the 2015–2017 era compared to all other eras combined (Mann-Whitney test; $p<0.001$).

[f] Conditions were significantly less frequent in the 2015–2017 era compared to all other eras combined (chi-square test; $p<0.001$).