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Impact of Pre-antiretroviral Therapy CD4 Counts on Drug Resistance and Treatment Failure: A Systematic Review

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Abstract

The continuous rising of HIV drug resistance in low- and middle-income countries and its impact on treatment failure is a growing threat for the HIV treatment response. This review aimed to document pre-antiretroviral therapy (ART) CD4 counts, emerging drug resistance, and treatment failure in HIV-infected individuals initiating ART. We performed an online search in PubMed, Embase, Web of Science, African Index Medicus, Cochrane library, and The National Institute for Health Clinical Trials Registry of relevant articles published from January 1996 to June 2019. Of 1755 original studies retrieved, 28 were retained for final analysis. Treatment failure varied between 5% (95% confidence interval [CI]: 2.7-7.4) and 72% (95% CI: 55-89.6), while resistance varied between 1% (95% CI: 0.47-1.5) and 48% (95% CI: 28.4-67.6). Participants with a pre-ART CD4 count below 200 cell/μl and low adherence showed higher percentages of resistance and failure, while those with CD4 count above 200 showed lower resistance and failure regardless adherence levels. Most frequent resistance mutations included the M184I/V for the nucleoside reverse-transcriptase inhibitors (NRTIs), K103N, and Y181 for the non-NRTIs (NNRTIs), and L90M for the Protease inhibitors. Pre-ART CD4 count and adherence to treatment could play a key role in reducing drug resistance and treatment failure. The increased access to ART in resources limited settings should be accompanied by regular CD4 count testing, drug resistance monitoring, and continuous promotion of adherence. In addition, the rising of resistance mutations associated with NRTIs and NNRTIs, suggest that alternative ART regimens should be considered. **(AIDS Rev. 2020;22:78-92)**

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Key words

Pre-antiretroviral therapy CD4 counts. Adherence. Resistance. Treatment failure.

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Introduction

With the increasing efforts of the United nation for HIV/Acquired Immune Deficiency Syndrome (AIDS) to scale up treatment[1,2], more and more HIV-infected individuals are expected to receive antiretroviral (ARVs) drugs for either treatment or prevention in the next coming years[3]. However, such efforts contrast with unreliable drug supply chains, drug stock-outs, high attrition of patients, poor adherence to treatment, low rates of viral suppression, and suboptimal use of viral load testing, especially in low- and middle-income countries (LMICs)[4]. For example, despite effective ARVs therapy (ART), viral failure occurs between 11.1% and 24% after 12 months ART initiation in many HIV-infected patients[5,6], and between 50% and 90% of patients with ART failure have evidence of resistance[7-9]. In addition, although CD4 declines occur more slowly in HIV-2 than in HIV-1 patients, the CD4 recovery with ARVs treatment is smaller in the former. Moreover, HIV-1 and HIV-2 differ in their ARV susceptibilities and drug resistance mutations (DRMs)[10] with HIV-2 being naturally resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and some protease inhibitors (PIs), yet susceptible to all nucleoside reverse transcriptase inhibitors (NRTIs) and integrase inhibitors. Furthermore, drug resistance in HIV-2 may develop earlier than in HIV-1 and select for mutations at distinct sites. That is among reasons why misdiagnosis of HIV-2 in patients wrongly considered as HIV-1 positive or in those dually infected may result in treatment failures with undetectable HIV-1 RNA[11]. The situation deserves special attention since these resistances are primarily driven by NNRTIs[6,12,13] which constitute the backbone of ART regimens in the majority of LMICs[14]. Pre-ART lower CD4 count[15,16] poor adherence to medications[17,18] suboptimal viral suppression[19] among others have been associated with odds of treatment failure and death, while initiation of ART at higher CD4 cell count has been associated with success in viral response, reduced risk of AIDS events, and death[17,20]. Thus, there is a need in understanding the role of pre-ART CD4 counts, as well as adherence to treatment in the emergence of drug resistance and treatment failure. The objective of this review was to document the impact of pre-ART CD4 counts, and adherence to treatment on emerging drug resistance, and treatment failure in HIV-infected individuals after ART initiation.

Methods

This review was reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The study protocol was registered with the PROSPERO database (CRD42018111592).

Eligibility criteria

We considered randomized controlled trials (RCT), cohort studies, and longitudinal studies that included: (1) HIV-infected adults (age ≥ 18) and documented (2) pre-ART CD4 count, (3) adherence to treatment, (4) resistance to at least one component of ART regimen, (5) treatment failure, and (6) was published in a peer-reviewed journal between January 1996, year of starting ART[21], and June 2019. Language restriction was not applied, and the English translation was sought when necessary. If two articles presented data from the same study and target population, the article with the longest follow-up was considered for analysis.

Data sources

A systematic search for published studies was performed in PubMed, Embase, Web of Science, African Index Medicus, Cochrane Library, The National Institute for Health Clinical Trials Registry, conference abstracts, and article references using appropriate keywords. Conference websites included Conferences on Retroviruses and Opportunistic Infections, International AIDS Society, International Congress on Drug Therapy in HIV Infection, and the International Drug Resistance Workshop. We also manually examined reference lists from relevant identified studies. Authors of studies with non-reported adherence and or pre-ART CD4 counts were contacted for detailed data.

Search strategy

The search strategy was developed and carried out by (MD and RA) assisted by our medical librarian expert (FB). For PubMed search, we used specific medical subject headings, title/abstract (ti, ab), and text words to identify relevant articles published from January 1996 to June 2019. The strategy used the following key words: "HIV," "CD4," "ART," "adherence," and "Drug resistance." Then, these five together were combined with "RCT" using "AND" or "Observational studies" using "AND." These five together were also combined with

("hiv PIs" OR "NRTIs" OR "Non-Nucleosides reverse transcriptase inhibitors") using "AND" and ("RCT;" or "Observational studies") using "AND." For the other database, appropriate search strategies were applied.

Data management

Selection process

Two independent reviewers MD and RA, separately screened ti/ab of potentially relevant articles using Distiller systematic review software (DistillerSR), online web-based software for systematic Review (University Michigan) in accordance with inclusion and exclusion criteria. In cases of divergence between reviewers, the agreement was reached by consensus with a third reviewer (CA). The DistillerSR software automatically computed Cohen's kappa coefficient (κ) which measures the inter-rater agreement. A kappa score of ≥ 85% was required before initiating the next step.

Data extraction process

Reviewers extracted data using a standardized form with authors, year of publication, country (ies) where the study was conducted, population characteristics (age, gender, and group of population), settings (community center, hospital clinic, multicenter), objectives, study design, sample size, CD4 count, ART regimens, duration of follow-up, measure of adherence, adherence levels, viral suppression (below quantification limits), drug resistance, and treatment failure. Our outcomes variables included pre-ART CD4, levels of adherence, drug resistance, and failure at the end of the study. We chose these variables because pre-ART CD4 count, levels of adherence were reported as predictors of drug resistance and treatment failure.

Quality of individual studies and risk of bias

Standardized quality assessment tools tailored to each study design was used to best assess methodological quality and risk of bias. The Cochrane guide for assessing the quality of RCT[22] was used to grade the quality of each individual RCT study as good, fair, or poor. For observational studies, the quality assessment tool by Nguyen et al. 1999[23] was used. Main domains assessed include population characteristics and settings, methods of investigation, and assessment of the outcome variables.

Data analysis

Data were synthesized using a narrative approach. Pre-ART CD4 count was categorized into ≤ 200 cell/μl versus > 200 cell/μl and levels of adherence into < 90% versus ≥ 90%. To better capture the overall rate of failure and drug resistance per adherence levels, studies were divided into two groups: a group of studies where more than 80% of participants had adherence levels above 90%, and a group of studies where more than 80% of participants had adherence levels below 90%. Treatment failure was defined as repeated viral load above detection limits, while resistance was defined as any reported mutation associated with drug resistance. The overall results are presented using tables and figures.

Results

Included studies

A total of 1755 unique citations were retrieved through electronic databases and hand search. We excluded 1100 studies after ti/ab screening, leaving 655 for full-text screening. Of these, 595 were excluded for the following reasons: no relevant data on pre-ART CD4 count (n = 80), resistance (n = 215), number of participants at ART initiation (n = 85), and resistance and treatment failure (n = 215). An additional 32 studies were excluded for incomplete data after multiple attempts to reach authors. In total, twenty-eight articles met inclusion criteria for qualitative synthesis. The characteristics of the included studies are shown in figure 1.

Studies characteristics

Studies were reported from 15 countries: Botswana[24], Cameroon[25,26], Cambodia[27], Canada[28-30], Côte d'Ivoire[31,32], Ethiopia[33], India[34-36], Nigeria[36], Senegal[37], South Africa[38,39], The UK[40], Uganda[41], USA[31,42-51], and France and Spain[45] and were published between 2001 and 2017. Of them, 13 were RCT[24,26,29,36,40,42-45,48-51], 12 cohort studies[25,27,28,32-35,37-39,41,46,47], and three longitudinal studies[27,28,31]. Follow-up varied between a minimum of 3 months[42] and a maximum of 84 months[47]. Seven studies had a follow-up duration between 3 and 12 months[31,32,39,41,42,44,50], ten between 13 and 24 mon ths[25,26,34-36,38,40,45,46,51], and the remaining above 24 months. Overall, the included studies summarized data from 18985 HIV-infected individuals.

Table 1. Summary of included studies

Author, year	Country	Study Design	ART regimens	Sample size	Pre-ART CD4 count (cell/µl)	Duration of follow up (months)	Measures of adherence	Adherence levels (%)	Definition of failure (Plasma viral load copies/mL)	Rate of failure (%)	Rate of resistance (%)
Mulu et al., 2015	ETHIOPIA	Prospective cohort study	ZDV, 3TC, D4T, NVP, EFV, ABC, TDF, ddI	220	204 (IQR: 26-203)	30 (IQR: 26-36)	Self-report	109 (49.5)	≥ 400 copies/mL	7	27
Pujades-Rodriguez et al., 2011	Cambodia	Longitudinal study	d4T, 3TC, NVP, EFV, AZT, TDF	349	16 (IQR: 4-71)	48	Visual analog scale	289 (82.8)	≥ 1000 copies/mL	32	3.1
Ford et al., 2010	South Africa	Cohort study	EFV-based, NVP-based	207	55 (IQR: 20-115)	24	Self-report	181 (87.4)	≥ 5000 copies/mL	15.4	NA
Oyugi et al., 2007	Uganda	Cohort study	Not reported	97	56 ± 130	6	Self-report, pill count, and EMM	82-95	≥ 1000 copies/mL	19.6	8.2
Uy et al., 2009	USA	Observational cohort study	NNRTIs, NRTIs, PIs	760	200	84	Not documented	NA	≥ 50 copies/mL	32	4.4
Adje-Toure et al., 2003	Cote-d'Ivoire	Longitudinal study	ZDV, 3TC, D4T, ddI, NFV, IDV, SQV	25	82 (IQR: 52-188)	11	Self-report	12 (48)	Not reported	72	48
Lockman et al., 2012	USA	RCT	NVP, TDF, FTC, LPV/r	500	121 (IQR: 38-204)	29.5	Self-report	390 (78)	≥ 400copies/mL	16	3.8
Laurent et al., 2005	Senegal	Prospective cohort study	NRTIs, NNRTI, PIs	176	144 (IQR: 58-224)	30 (IQR: 21-36)	Self-report	155 (95)	≥ 1000 copies/mL	NA	12.5
Messou et al., 2011	Cote-d'ivoire	Prospective cohort study	d4T, 3TC, FTC, EFV	996	148 (IQR: 68-229)	12	Medication possession ratio	693 (69.7)	≥ 300 copies/mL	23.2	4.5
Laurent et al., 2008	Cameroon	Prospective cohort study	NNRTIs, PIs	169	152 (IQR: 67-223)	24	Not documented	NA	≥ 1000 copies/mL	14	6.5
Maitland et al., 2005	USA	RCT	To be found	77	158 (IQR: 8-572)	3	Medication Event Monitoring System (MEMScap)	77 (100)	≥ 1000 copies/mL	NA	6.5

(Continue)

Table 1. Summary of included studies (*Continued*)

Author, year	Country	Study Design	ART regimens	Sample size	Pre-ART CD4 count (cell/μl)	Duration of follow up (months)	Measures of adherence	Adherence levels (%)	Definition of failure (Plasma viral load copies/mL)	Rate of failure (%)	Rate of resistance (%)
Coker et al., 2015	Nigeria	RCT	d4T, ZDV, TDF	600	150	18	Self-report, cumulative pharmacy (Rx) refill rates	133 (21.17)	≥ 1000 copies/mL	6.3	1.3
MacArthur et al., 2006	USA	RCT	NFV, IDV, RTV, LPV, EFV, NVP, ZDT, 3TC, d4T, ddI, ABC	1397	162.5	32	Self-report	1383 (99)	≥ 1000 copies/mL	62	1
Lima et al., 2008	Canada	Longitudinal study	NNRTIs, PIs	878	165 (IQR: 70-270)	44	Prescription refill	547 (62.33)	≥ 1000 copies/mL	NA	18.6
Asboe et al., 2007	The UK	RCT	ddI, d4T, ZDV, 3TC, NVF, EFV, NFV, LPV/r, IDV	124	145 (IQR: 73-235)	20	Self-report	103 (83)	≥ 400copies/mL	30	10.5
Boulle et al., 2013	Cameroon	RCT	d4T, 3TC, NVP, EFV, ZDV	456	181 (IQR: 87-336)	24 (IQR: 18-24)	Self-report	155 (34)	≥ 5000 copies/mL	13	9.8
Bussmann et al., 2009	Botswana	RCT	ZDV, 3TC, ZDV, ddI, d4T, NVP, EFV	650	199 (IQR: 136-252)	26	Self-report	506 (77.8)	≥ 400 Copies/mL	8.4	6
Markowitz et al., 2005	USA	RCT	ABC, 3TC, ZDV, EFV	448	210 (IQR: 24-197)	12	Self-report	237 (53)	≥ 500 copies/mL	5	2.2
Molina et al., 2007	USA France, UK Spain	RTC	NVP, TDF, FTC, LPV/r	190	214 (IQR: 3-965)	24	Medication Event Monitoring System (MEMS)	190 (100)	≥ 500 copies/mL	25	2.1
Orrell et al., 2017	South Africa, USA	Cohort study	EFV, NVP, TDF, ZVD, d4T	230	225 (IQR: 133-287)	12	Self-report, pill count, and pharmacy refill	230 (100)	≥ 400 copies/mL	6	4.3

(Continue)

Table 1. Summary of included studies (*Continued*)

Author, year	Country	Study Design	ART regimens	Sample size	Pre-ART CD4 count (cell/μl)	Duration of follow up (months)	Measures of adherence	Adherence levels (%)	Definition of failure (Plasma viral load copies/mL)	Rate of failure (%)	Rate of resistance (%)
Gathe et al., 2011	USA	RCT	NVP, TDF, FTC	1013	228±83.6	12	Pill count	NA	≥ 400 copies/mL	5.3	5
Daar et al., 2011	USA	RCT	ABC, 3TC, TDF, FTC, EFV, ATV, RTV	1850	230 (IQR: 90-334)	34.5 (26-42)	Self-report	1671 (90.3)	≥ 1000 copies/mL	14.5	13
Cohen et al., 2013	USA	RCT	RPV, EFV, FTC, TDF, ZDV, 3TC, ABC	1368	260 (IQR: 118-137)	24	MMASRI adherence	1051 (76.8)	≥ 1000 copies/mL	9.3	10.8
Wood et al., 2005	Canada	NRCT	NNRTIs, NRTIs, PIs	1191	270 (IQR: 110-420)	37	Prescription refill	NA	≥ 1000 copies/mL	NA	25
Lima et al., 2015	Canada	Retrospective cohort study	NNRTIs, PIs	4120	200	60	Prescription refill	3219 (78.13)	≥ 250 copies/mL	NA	10.8
Ekstrand et al., 2011	India	Cohort study	3TC, d4T, NVP, AZT, EFV, FTC, TDF, PIs	551	348 (IQR: 222-476)	24	Visual analog scale	145 (26.3)	≥ 1000 copies/mL	24	16.7
Neogi et al. 2013	India	Observational cohort study	d4T, 3TC, NVP, AZT, EFV, FTC, TDF, DDI	323	370 (IQR: 243-525)	23	Visual analog scale	243 (75.2)	≥ 400 copies/mL	5	2.8
Berrey et al., 2001	USA	Cohort study	ZDV, 3TC, IDV	20	650 (IQR: 257-1199)	24.5 (15-17)	Pill count	96	HIV-1 RNA ≥ 50 copies/mL	NA	10

ART regimens; ZDV: zidovudine, 3TC: lamivudine, D4T: stavudine, ddI: didanosine, NFV: nelfinavir, SQV: saquinavir.
Adherence levels: number (%) of participants with adherence level. Pre-ART CD4 count: mean/median CD4 count before ART initiation. Definition of treatment failure: treatment failure was defined as repeated viral loads above detection limits (plasma viral load copies/mL). Percentage of failure: percentage of failure was calculated using number of failures that occurred during the study follow up reported to the number participants that initiated the treatment. Percentage of resistance: percentage of resistance was calculated using number of cases of resistance that occurred during the study follow up reported to the number participants that initiated the treatment.

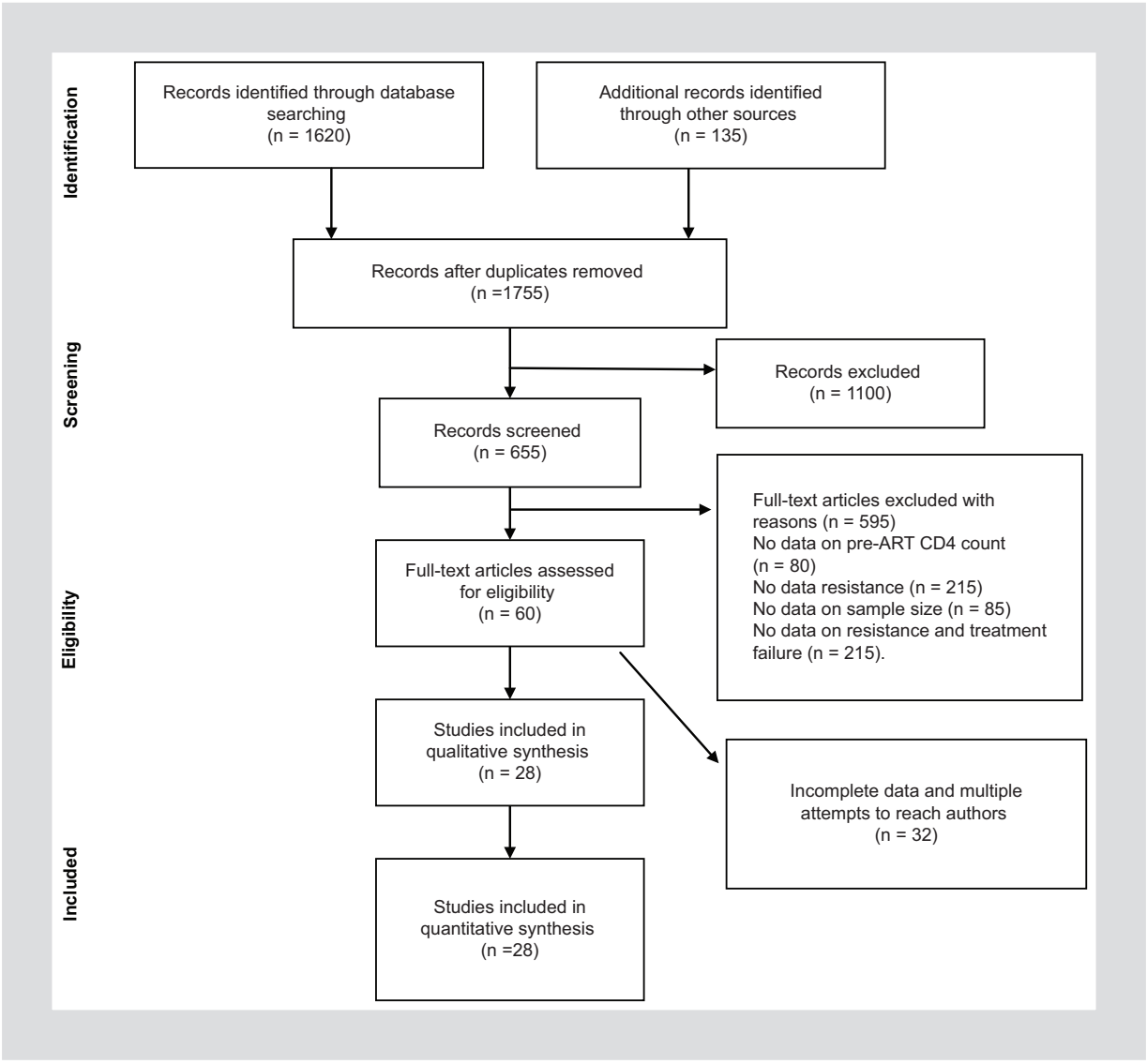

Figure 1. *PRISMA flow diagram of the study selection process (search is updated to 2019).*

The pre-ART $\log_{10}$ viral load varied between 4.4 and 5.53 copies/ml. Threshold for treatment failure ranged from ≥ 50 copies/ml[46,47], ≥ 250 copies/ml[30], ≥ 300 copies/ml[32], ≥ 400 copies/ml[24,33,35,39,48,50], ≥ 500 copies/ml[44,45], ≥ 1000 copies/ml[25,27-29,34,36,41-43,49,51], and ≥ 5000 copies/ml[26,38]. Methods used to measure adherence to treatment included self-report[24,26,31,33,37,38,40,43,44,48,49], pill count[46], prescription refill[28,30], visual analog scale[27,34,35], combination of methods such as self-report, pill count, and EMM[41], self-report, cumulative pharmacy (Rx) refill rates[36], self-report, pill count, and pharmacy refill[39], (Table 1).

Population characteristics and settings

All participants were adults recruited from hospitals and clinics and started treatment for the 1st time. The median sample size was 452 participants, with a median age of 37 years, among whom 65% were women. Four studies had a sample size below 50 participants[31,46], two between 50 and 100 participants[41,42]. The overall median CD4 cell count was 225 (interquartile range [IQR] 125-324) cells/μl and that of plasma viral load was 5.0 (IQR 4.6-5.4) $\log_{10}$ copies/mL. Four studies had pre-ART CD4 count below 100 cells/μl[27,31,38,41], 11 between 100 and 200 cells/μl[24-26,28,32,36,37,40,42,43], the rest of studies above 200 cells/μl (Table 1). The median duration of follow-up was 24 months with a minimum of 3 months and a maximum of 84 months. Classification of studies according to the number of participants with adherence levels above 90% revealed that in 11 studies, more than 80% of participants reported adherence levels above 90%[27,37-43,45,46,49], while in 13 studies, more than 80% of participants reported adherence levels below 90%. The traditional combination of two NRTIs with one NNRTIs regimen was used in the 20 studies, while in eight

Table 2. Index of drug resistance

Author/year	Country	Sample size	CD4 count	Mean/median Viral Load (Log_{10}Copies/mL)	Adherence levels	NRTIs	NNRT	PIs
Mulu et al., 2015	Ethiopia	220	≥ 200	4.4 (IQR:3 .6-5.1)	< 80%	M184V, K65R	V106M, K103N, Y181S, Y188L, V90I, K101E, G190A	
Pujades-Rodriguez et al., 2011	France, Cambodia	349	< 200	NA	≥ 80%	F116FY, Q151LM, D67N, K70KR, M184V, T215Y, T215F, T69N, M41L, D67N, T69D, L74V, L210W, T215Y, K70R, T215I, K219E, K65R	Y181C, K103N, P225H, K101E, G190A, M230L, L100I	
Ford et al., 2010	South Africa	207	< 200	5.03 (IQR: 4.3–5.5)	≥ 80%	NA	NA	NA
Oyugi et al., 2007	Uganda	97	< 200	5.53 ± 5.8	≥ 80%	M184V, K65R, F77L, Q151M, M41L, M36I, R211K, L214F	Y181C, K103N, G190A	
Uy et al., 2009	USA	760	≥ 200	4.90 (IQR: 4.4–5)	NA	M184V, M41L, K65R	Y181C, K103N, G190A	L90M
Adje-Toure et al., 2003	Côte d'Ivoire	25	< 200	4.5 (IQR,4.1–5.2)	< 80%	Q151M, S215Y, M184V, M184V/I, M184I, Q151M, G48V, K70N	S215Y, F221Y, G48V, Q151M, K70N, M184V, M184I	L90M
Lockman et al., 2012	Botswana, Uganda, Zambia, USA	500	< 200	5.15 (IQR: 4.2, 5.9)	< 80%	K65R, K70W, M184V	K103N, V106A, V106M, V108I, Y181C, Y181I, Y188C, G190A	
Laurent et al., 2005	Senegal	176	< 200	5,30 (IQR: 4.8–5.6)	≥ 80%	M184V, M41L, K65R	Y181C, K103N, G190A	L90M
Messou et al., 2011	Cote d'ivoire	996	< 200	NA	< 80%	M184V/I 41L, 210W, 215Y, 67N, 70R, 219E/Q	Y181C, K103N, G190A	
Laurent et al., 2008	Cameroon	169	< 200	5.2 (IQR: 4.7–5.5)	NA	M184V, M184M/V, M41L/M, T215Y, M36I, A71T	K103N, Y188C/Y, Y181C, G190A	L90M
Maitland et al., 2005	United Kingdom	77	< 200	4.99 (IQR: 4.78–5.22)	≥ 80%	103N, 225H, 188L, 108I, 103T, 65R, 74V,190S,190E/S, 100I, 179D	108I, 190E/S, 188L, 100I, 179D, 225H	

(Continue)

Table 2. Index of drug resistance (*Continued*)

Author/year	Country	Sample size	CD4 count	Mean/median Viral Load (Log_{10}Copies/mL)	Adherence levels	NRTIs	NNRT	PIs
Coker et al., 2015	Nigeria	600	< 200	4.7 ± 1.3	< 80%	M184V, K65R, 41L, 210W, 215Y, 67N, 70R,219E/Q	Y181C, K103N, Y188C/Y, G190A	
MacArthur et al., 2006	USA	1397	< 200	5.15 (IQR: 4.6-5.6)	≥ 80%	M184I/V	L103A, T181C/I, G190A/S	A30A, L33I/P, L90M
Lima et al., 2008	Canada	878	< 200	5.0 (IQR: 4.7–5.1)	< 80%	184I/V, 41L, 62V, 65R, 67N, 69D, 70R, 74V, 75I, 151M, 210W, 215F/Yor 219E/Q	100I, 103N, 106A/M, 108I, 181C/I, 188C/H/L, 190A/S, P225H, M230L or 236L	30N, 46I/ L, 48V, 50L/V, 54V/L/M, 82A/F/S/T, 84V, or 90M
Asboe et al., 2007	United Kingdom	124	< 200	4.92 ± 0.62	≥ 80%	M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, and K219Q/E	K103N, Y188L, V106M, Y181C/I, V108I, P225H	
Boulle et al., 2013	Camerron	456	< 200	5.6 (IQR, 5.2–6.1)	< 80%	M184V, M184V/I	K103N, Y181C	
Bussmann et al., 2009	Botswana	650	< 200	5.3 [IQR 4.8-5.6]	< 80%	67N, 70R, 215Y, T215Y, M41L, 215Y	K103N/S, V106A/M, Y181C/I/V, Y188L/C/H, and G190A/S/E, Y188L, G190S	
Markowitz et al., 2005	USA	448	≥ 200	5.08 (IQR:1.69–6.86)	< 80%	M184V, M41L, D67N, L210W, T215Y, D67D/N, V118V/I, K65R, V118I, M184V/M, K70R, L210W, T215Y/F, K219Q/E, D67D/N, K70R/K, K219E/K	K103N, Y188L, P225H, G190S, Y188H/Y, P225P/H	
Molina et al., 2007	USA France, UK Spain	190	≥ 200	4.6 (IQR:2.6–6.2)	≥ 80%	M184V/I		
Orrell et al., 2017	South Africa, USA	230	≥ 200	4.9 (IQR:4.4–5.4)	≥ 80%	M184V, K65R, L100I, K101E	L100I, K101E, K103N, V106M, Y181C, Y188C/Y/L, G190A/G/S, H221HY, V90I, E138A, V179D, H221HY, F227L	

(Continue)

Table 2. Index of drug resistance (*Continued*)

Author/year	Country	Sample size	CD4 count	Mean/median Viral Load (Log_{10}Copies/mL)	Adherence levels	NRTIs	NNRT	PIs
Gathe et al., 2011	USA, UK, Argentina, South Africa,	1013	≥ 200	4.7 ±0.7	NA	M184I/V, M184V, M184I, K65R/N	Y181C	
Daar et al., 2011	USA	1850	≥ 200	4.7 (IQR: 4.3–5.0)	≥ 80%	M184I/V, K65R, L74I/V	K103N, Y181C, L100I, G190A/E/Q/S	
Cohen et al., 2013	USA, France, China	1368	≥ 200	5 (2–7)	< 80%	M184I/V, M184I, L100I, A62 V, K65R, Y115F, K219E, M184V, V108I, Y188C	E138K, K103N, V90I, L100I, K101E, E138Q, V179I, Y181C, V189I, H221Y, F227C, V106 M, V108I, Y188C	
Wood et al., 2005	Canada	1191	≥ 200	5.1 (IQR: 4.6–5.5)	NA	184I/V, 41L, 62V, 65R, 67N, 69D, 70R, 74V, 75I, 151M, 210W, 215F/Y, 219E/Q	100I, 103N, 106A/M, 108I, 181C/I, 188C/H/L, 190A/S, P225H, M230L, 236L	30N, 46I/L, 48V, 50L/V, 54V/L/M, 82A/F/S/T, 84V, 90M
Lima et al., 2015	Canada	4120	≥ 200*	4.90 (IQR: 4.38–5.00)	< 80%	M184V/I, 41L, 62V, 65R, 67N, 69D or insertion, 70E/R, 74V, 75I, 77L, 115F, 116Y, 151M, 210W, 215F/Y or 219E/Q	100I, 101E/H/P, 103N, 106A/M, 108I, 138A/G/K/Q/R, 181C/I/V, 188C/H/L, 190A/S, 225H, 230L or 236L	30N, 32I, 33F, 46I/L, 47A/V, 48V, 50L/V, 54V/L/M, 58E, 74P, 76V, 82A/F/L/S/T, 84V, 88S, 90M
Ekstrand et al., 2011	India	551	≥ 200	NA	< 80%	M184V/MV/I/IM, E44D/DE/A/K, L74V, V75M, V118I, T69D/DN, K65R, Q151M, T215Y, M41L/LM, L210W, T215F, D67N/DN, K70R/KR/E, K219E/Q	Y181C/CY/I/V, K103N/KN/R, K101E/EK/Q/KQ, G190A/AG, V108I, A98G, V106M/MV, V90I, Y188L, E138K/EK	
Neogi et al. 2013	India	323	≥ 200	NA	< 80%	M184V, K70R, K65R	G190A, V108I, Y181C, H221Y, K103N, V108I, H221Y, A98G, K101E, Y181C, H221Y, K101E, V106M	
Berrey et al., 2001	USA	20	≥ 200	4.6 (IQR: 2.8–5.6)	≥80%	T215F, K70R, T69N, T215D, M41L, M41L		

NRTIs: Nucleoside Reverse Transcriptase Inhibitors; NNRTIs: Non-nucleoside Reverse Transcriptase Inhibitors; PIs: Protease inhibitors; NA: Not Available. Adherence ≥ 80%: represent studies in which more than 80% of participants reported adherence above 90%. Adherence < 80%: represent studies in which more than 80% of participants reported adherence below 90%.

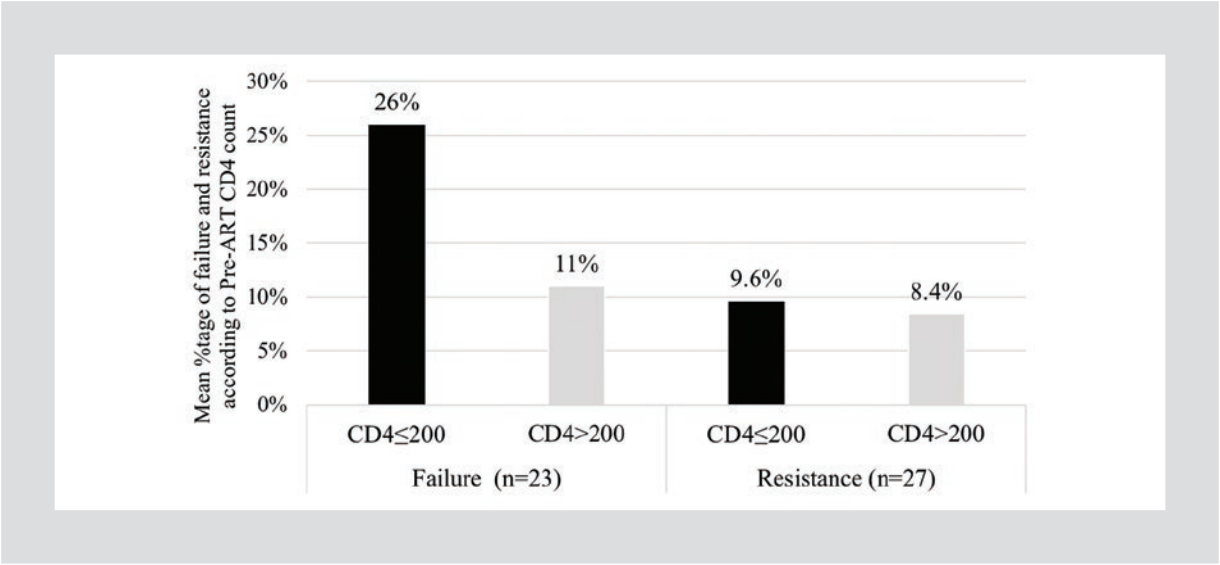

Figure 2. *Percentages of failure and resistance according to pre-antiretroviral therapy CD4 count.*

studies[25,28-31,37,43,47], the third class of drug, the PIs were included (Table 2).

Percentage of failure

The overall percentages of failure varied between 5% (95% confidence interval [CI]: 3.0-7.0)[35] and 72% (95% CI: 55-89.6)[31] with a mean of 21% (Fig. 2). Eight studies[24,33,35,36,39,44,50,51] showed a percentage of failure below 10%, seven[25,26,28,38,41,48,49] between 10% and 20%, and four[27,31,40,43] above 30%. All studies with a pre-ART CD4 count below 200 cell/μl showed percentages of failure above 10%, while those with a pre-ART CD4 above 200 cell/μl showed percentages of failure below 10%. Studies with highest failure rates were from Côte d'Ivoire 72% (95% CI: 55-89.6)[31], USA 62% (95% CI: 59.5-64.5)[43], and Cambodia 32% (95% CI: 27-37)[27].

Percentage of drug resistance

Likewise, percentages of emerging resistance per individual study were estimated using the number of participants who showed mutations associated with resistance reported to the number of participants who initiated the treatment at the start of the study. Percentages of resistance varied between a minimum of 1% (95% CI: 0.47-1.5)[43] and a maximum of 48% (95% CI: 28.4-67.6)[31] with a mean of 9% (Fig. 2). In 19 studies, 11 with a pre-ART CD4 count below 200 cell/μl, and eight with a pre-ART CD4 above 200 cell/μl showed resistance below 10%. In seven studies[28-30,34,37,49,51], three with a pre-ART CD4 count above 200 cell/μl[29,34,49] showed resistance between 10 and 20%. Resistance rates higher than 20% were observed in only two studies 25% (95% CI: 22.5-27.5) and 48% (95% CI: 28.4-67.6)[29,31].

Pre-ART CD4 count, adherence, and resistance

The overall percentages of failure were higher compared to resistance in all studies. In addition, studies with a pre-ART CD4 count below 200 cell/μl showed higher percentages of failure, and resistance (Fig. 2) compared to studies with a pre-ART CD4 count above 200 cell/μl. Likewise, percentages of failure and resistance were higher in studies where more than 80% of the participants reported an adherence level below 90% (Fig. 3). Three studies[27,40,43] with a pre-ART CD4 count below 200 cell/μl and more than 80% of participants reporting adherence above 90% had a percentage of failure above 30%. In five studies[38,41,45,46,49], in which more than 80% of participants reported adherence above 90%, percentages of resistance ranged between 10 and 20%. In five studies[31,35,39,50,51] with a pre-ART CD4 count above 200 cell/μl and adherence levels below 90% for more than 80% of the participants, percentages of failure were below 10%.

Among seven studies with adherence level above 90% for more than 80% of the participants and pre-ART CD4 count below 200 cell/μl, six[27,37,40-43] showed percentages of resistance below 10%. In six studies

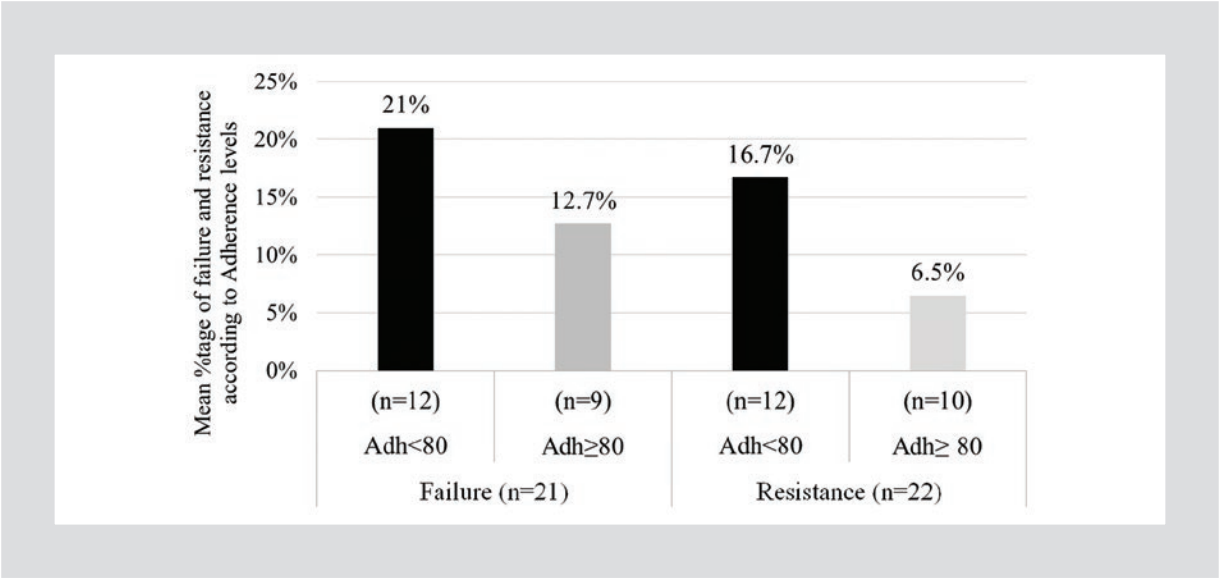

Figure 3. *Percentage of failure and resistance according to adherence.*

with adherence levels below 90% for more than 80% of the participants and pre-ART CD4 count above 200 cell/μl, four[24,33,35,44] showed percentages of resistance below 10%, while two, Ekstrand et al., 16.7% (95% CI: 13.7-19.8)[34] and Cohen et al. 10.8% (95% CI: 9.1-12.4)[51] showed percentages above 10%.

Discussion

Our analysis revealed that pre-ART low CD4 count (below 200 cell/μl), and adherence levels (below 80%) as determinant predictors of drug resistance and treatment failure. Indeed, following ART initiation, most patients with a pre-ART low CD4 count are at high risk of treatment failure due to uncontrolled immune response such as immune reconstitution inflammatory syndrome (IRIS) that occurs following ART initiation. In this context, many studies have shown that pre-ART low CD4 count (under 100 cells/μl)[52] and CD4 percentage (below 15%)[53] were associated with a greater risk of developing IRIS by nearly 3-time compared to CD4 percentage over 15%. Thereby, the higher percentages of failure observed in our studies with pre-ART CD4 count below 200 cell/μl could be, at least in part, explained by such a situation. Other factors such as duration of ART[54], low pre-ART CD4 cell count[55], poor adherence[56], repeated viral load above 1000 copies/mL[57], low levels of viremia[58], drug toxicity,[59] and drug resistance[60] could also explain these rates of failure.

It is obvious that CD4 cells do not directly induce the development of drug resistance since there is no known pattern from CD4 cells that interact with the drugs and induce drug resistance. However, their levels at ART initiation could facilitate the development of drug resistance and treatment failure. Schultze et al. 2018 showed that the detection of any resistance to NNRTI, the RT mutations V179D and L74V were associated with steeper CD4 cell declines. Likewise, the presence of some mutation patterns similar to the clusters identified by the PCA also affected the CD4 cell decline[61]. Moreover, certain polymorphic protease substitutions could also be associated with CD4+ cell declines and lower viral load set points[62]. With the high prevalence of transmitted rug resistance in LIMICs, this process could play an important role not only in the increase of DRMs, but also in the CD4 decline. Furthermore, the fact that HIV-2 is naturally resistant to both NNRTIs and some PIs and given the relatively large number of people living with HIV-2 infection in the Western African region, HIV-1/HIV-2 coinfection should always be excluded at first diagnosis in all HIV-seroreactive persons[63].

With regards to adherence, our results showed that studies with higher adherence levels had lower percentages of drug resistance and failure, while those with lower adherence levels had higher percentages of resistance and failure. Although great improvements in access to ART have been achieved in the recent years with a global ART coverage that has more than

doubled from 2010 to 2015[64], strong gaps related to unreliable drug supply chains, drug stock-outs, and above all high attrition of patients, still remain[65]. Considering that the global estimates of non-adherence to ART vary between 2% and 70%[66] in adults, 16% and 99%[67] among adolescents in LMICs, HIV-infected individuals need to be highly adherent to treatment to achieve viral suppression, and avoid drug resistance and treatment failure.

The most prevalent resistance mutations observed in our review were the M184V/I mutation associated with the NRTIs; the Y181C, and K103N, associated with NNRTIs; and the L90M associated to the PIs (Table 1). Globally, in LMICs, HIV treatment has long-time been composed of the dual NRTI/NNRTI-based regimens. In the recent years, pre-treatment drug resistance related to these classes of drugs has been increasing and becomes a real threat for the success of HIV treatment especially in LIMICs[68]. A recent study by the World Health Organization in LMICs found that prevalence of NNRTI pre-treatment drug resistance higher in women compared to men in Africa, South America, and Southeast Asia, that of NRTI > 10% in women, but < 10% in men; while that of PI was < 5% in all countries[69]. For NNRTIs alone, a systematic review summarizing data from 63 countries found that prevalence of pre-treatment resistance in 2016 was 11.0% in Southern Africa, 10.1% in Eastern Africa, 7.2% in Western and Central Africa, and 9.4% in Latin America and the Caribbean. Furthermore, the yearly increases in the odds of pre-treatment drug resistance were 23% in Southern Africa, 17% in Eastern Africa, 17% in Western and Central Africa, 11% in Latin America and the Caribbean, and 11% in Asia[70]. The increasing prevalence of resistance mutations associated to these two classes of drug adds another obstacle to the effectiveness of ART in the HIV response. Therefore, addressing drug resistance remains a cornerstone for the effectiveness of ART in HIV response especially in LMICs. Current ART allows to achieve and sustain maximal suppression of HIV replication in most treated patients, unfortunately, drug adherence is often suboptimal and tends to decline over time. In this perspective, long-term ART either as "treatment as prevention" for HIV carriers or "pre-exposure prophylaxis" for uninfected individuals at risk could be a potential alternative to overcome the challenge of suboptimal drug adherence and reduce the burden of HIV infection[71]. Long-acting formulations of ARVs, that could potentially replace daily tablets, have been developed and are under investigation for prevention and treatment of HIV infection[72].

The four key points raised in this review, namely, the pre-ART CD4 count, adherence to treatment, drug resistance, and treatment failure, suggest that deep changes need to be undertaken in different levels of the treatment process to make the HIV response more effective especially in LIMICs.

First, increasing HIV testing coverage will help identify people living with HIV who need immediate treatment, facilitate referral to health care, and promote adherence to treatment. In this direction, promoting the HIV self-testing kit could play an important role in addressing gaps in HIV testing coverage and prevention services[73]. Second, since access to ART alone does not guarantee sustained viral suppression, routine CD4 testing coupled with periodic viral load monitoring could inform on treatment failure and help guide for resistance testing. Finally, promoting adherence to treatment at all levels of the treatment process will help achieve high levels of viral suppression and reduce the incidence drug resistance.

Conclusion

Although CD4 count may not directly induce drug resistance, pre-ART CD4 count and adherence levels could be determinant predictors of drug resistance and treatment failure. Therefore, the increased access to ART especially in resources limited settings should be accompanied with regular CD4 count testing, drug resistance monitoring, and continuous promotion of adherence. In addition, the rising of resistance mutations associated with NRTIs and NNRTIs, suggest that alternative ART regimens should be considered.

Authors' contributions

MD designed the study and retrieved the articles; FB helped constructing the key words in research databases; RA, CA, PN, and BAL helped with data extraction; MD and RA conducted data analysis, MA drafted the first draft. All coauthors revised and approved the final version.

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