ORIGINAL ARTICLE

Poorer early treatment outcomes among Human Immunodeficiency Virus -1 infected patients initiating antiretroviral therapy in the "test and treat" era in Nigeria

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Abstract

Background: Antiretroviral therapy (ART) initiation timing has undergone changes over time, with updates to recommendations for same-day ART initiation. The objective of this study was to compare early treatment outcomes in a large Nigerian ART center between the pre-"test and treat" and "test and treat" eras.

Methods: The study was a retrospective cohort analysis of 1782 patients who started ART in the pre-"test and treat" era (prior to April 1, 2017) and the "test and treat" era (April 1, 2017, to December 31, 2019) at the Jos University Teaching Hospital (JUTH) ART clinic. Data were extracted from an electronic medical record system. Multivariable logistic regression identified predictors of early immunologic and virologic failure.

Results: Of the participants, 1452 (81.4%) were in the pre-"test and treat" group, and 330 (18.5%) were in the "test and treat" group. Patients in the "test and treat" group had a higher proportion of early immunologic failure (58%) compared to the pre-"test and treat" group (37%). The odds of early immunologic failure were higher in the "test and treat" era (OR 5.88; 95% CI 3.29-10.52). Patients in the "test and treat" era had three times greater odds of early virologic failure (OR 3.46; 95% CI 1.70-7.01).

Conclusions: The study found that the "test and treat" strategy resulted in poorer early immunologic improvement and viral suppression compared to the era of CD4+ cell count guided treatment initiation. Additional interventions may be necessary to improve the effectiveness of the "test and treat" strategy, particularly in resource-limited settings.

Keywords: HIV, ART, test and treat, treatment outcomes, Nigeria

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Introduction

Nigeria is third on the list of nations with the greatest burden of HIV infection worldwide, with an estimated 1.9 million people living with HIV(PLHIV) as of 2018. Only about 30% of the PLHIV in Nigeria were on antiretroviral therapy (ART) at the end of 2017.[2] Prior to the "test and start" era, the timing of ART initiation was essentially a risk/benefit decision, with the benefits of early initiation outweighing the risks over time, leading to significant changes in recommendation for when to start ART.[3]

According to an International AIDS Society-USA Panel report, during the first 10 years of ART, the ART-start threshold fluctuated. The threshold for treating asymptomatic adults was 200 CD4+ cell/mm3 at the beginning of the 2000s.[3] Between 2006 and 2009, the ART-start threshold was raised to 350 CD4+ cell/mm^3 worldwide. Between 2009 and 2013, most guidelines further set the threshold to 500 CD4+ cell/mm.[3,3-4] By 2015, all international guidelines recommended commencing ART in all persons living with HIV (PLHIV) regardless of their CD4+ cell count.[5-8] There were some barriers to the implementation of this recommndation including a sudden surge in the numbers of PLHIV eligible for treatment as well as the increased numbers of healthcare workers needed to support service delivery. With the foregoing, the ART paradigm can be said to be in two eras; the era during which CD4+ cell count was used to determine ART eligibility (this prior to 2016), and the the era during which population at risk is screened and all PLHIV became eligible for ART irrespective of CD4+ cell count (2016 onwards). The WHO "test and treat" strategy was adopted by the Nigerian National Guidelines for HIV prevention, treatment and care in 2016. [9-10]

Virologic suppression, immunologic improvement, and retention in care are important patient-level outcomes which are useful in the evaluation of any ART programme. Virologic suppression is the third component of the UNAIDS 95-95-95 targets.[11] The AIDS Prevention Initiative in Nigeria, LTe (APIN) supported-centre, at the Jos University Teaching

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Hospital (JUTH), Jos, Nigeria began implementation of the "test and treat" guidelines on 1st April 2017. The aim of the study therefore was to determine and compare early treatment outcomes between the pre- "test and treat" and "test and treat" eras among PLHIV enrolled for care and treatment at JUTH.

Patients and Methods

Study Area

The Jos University Teaching Hospital is a 530-bed tertiary health institution located in Jos, Plateau state, Nigeria. The PEPFAR/APIN-supported ART programme is an outpatient clinic, and is one of the largest providers of treatment, care, and support to PLHIV in Nigeria. It offers comprehensive HIV services namely HIV testing services, adult and paediatric ART, prevention of mother-to-child transmission (PMTCT) of HIV, cervical cancer screening and family planning services and a robust laboratory support.

Study Population

The study was carried out among adult PLHIV who were enrolled and receiving ART at the clinic. . PLHIV were grouped into two categories; those who initiated ART from 1st January 2010 to 31st March 2017 (pre- "test and treat" group) and those initiated ART from 1st April 2017 to December 2019 ("test and treat" group) were included. Participating PLHIV had to be 18 years and above; receiving ART at the adult clinic during the study period and had to have given consent for their data to be used for research. PLHIV who had incomplete CD4 cell count and viral load data at twelve months were excluded in the end point analysis.

Study Design

The study was a retrospective cohort study that compared viral load suppression and immunological improvement 12 months after commencing ART; between cohorts of patients enrolled between 1st January 2010 to 31st March 2017 (pre- "test and treat" era) and those enrolled from 1st April to 30th December 2019 ("test and treat" era).

Definition of Terms

Pre- "test and treat" era in this study refers to the period from 1st January 2010 to 31st March 2017 (after which JUTH ART programme began implementation of the "test and treat" guidelines), while the *"test and treat"* era is the period from 1st April 2017 onwards.

Virologic failure: viral load above 1000 copies/mL based on two consecutive viral load measurements 3 months apart; with adherence support following the unsuppressed viral load test, after at least six months of ART .

Immunological failure: was defined as CD4+ cell count drop to the baseline (or below) or persistent CD4+ cell count levels below 100 cells/mm3 or 50% drop from peak CD4 count.

Data Collection

Demographic (sex, age, marital status, education, and occupation), clinical (mode of HIV transmission, WHO HIV disease stage, Hepatitis B or C co-infection, TB co-infection), and laboratory (CD4 cell count, viral load) and prescription records (first and last ARV dispense date, type of ARV regimen) were extracted from an electronic database maintained in the HSPH/APIN program (FileMaker Pro, v10; FileMaker, Inc, Santa Clara, California, USA). The extracted data was exported to Microsoft Excel for data cleaning.

Data Analysis

All of the analyses were performed using IBM SPSS for windows version 23 (IBM Corp, Armonk, New York, USA). Frequencies and proportions were reported for categorical variables, while continuous variables such as age, CD4+ cell count, and viral load were reported as median with interquartile range (IQR). An initial exploratory analysis revealed the skewed distribution of age, CD4+ cell count, and viral load data. Bivariate analysis of factors associated with immunologic and virologic failure was performed using Pearson Chi-Square. For the bivariate analysis, age was categorized based on age quartiles, CD4+ cell count based on WHO immunological HIV disease staging (Gilks et al., 2006; WHO, 2010, 2013, 2016), while viral load was categorized as $\leq$ 10,000, 10,001-100,000, >100,000 according to a strata used in a previous study in a similar setting. Baseline characteristics that were significantly associated with early immunologic and virologic failure in the bivariate analysis ($p < 0.05$), as well as those that were clinically relevant or had biological plausibility to affect immunologic and virologic outcomes, were included in a multivariable logistic regression model to identify independent predictors of early immunologic and virologic failure. The pattern of missing data was examined and determined to be missing at random, therefore a complete case analysis was used in the multivariate analysis to reduce bias due to missing data, while time varying covariates such as time on ART were not included in the logistic model.

Ethical Consideration

All patients enrolled into the JUTH HIV programme provided informed consent forms for their data to be used for HIV and other research. Ethical approval for the study was obtained from the JUTH Ethics Committee. Permission to conduct the study in the clinic and access

patients' data was sought from the Principal Investigator of JUTH APIN Centre.

Results

Participants' Selection and Characteristics

A total of 1,784 patients out of 3,342 (53%) were included in the study after meeting the inclusion criteria. Of these, 1,452 (43%) initiated ART before the "test and treat" era, while 332 (23%) began treatment during the "test and treat" period. The majority of participants were females (65%), and the median age at ART initiation was 33 years. No significant difference in gender was observed between participants in the pre- and post-test and treat era. However, participants in the pre-test and treat era were younger than those in the post-test and treat era.

Table 1: Distribution of Baseline demographic and clinical characteristics of study participants stratified by treatment period at the Jos University Teaching Hospital ART clinic (n=1782)

Variable	Pre-test and treat 1452 (81.4%)[a]	Test and treat 330 (18.5%)[b]	All patients 1782 (100%)	P value [a] versus[b]
Sex				
Female	952 (65.6)	205 (62.1)	1157 (64.9)	0.231
Male	499 (34.4)	125 (37.9)	624 (35.1)	
Missing data	1 (0.07)	0 (0)	1 (0.1)	
Age, years				
<29	480 (33.1)	78 (23.6)	554 (31.1)	<0.001
30-39	575 (39.7)	125 (37.9)	704 (39.5)	
40-49	289 (19.9)	90 (27.3)	379 (21.3)	
50-59	77 (5.3)	28 (8.5)	105 (5.9)	
≥60	29 (2.0)	9 (2.7)	38 (2.1)	
Median (IQR)	33 (28 - 39.3)	38 (31.5 - 46.5)	33 (28 - 40)	<0.001
Employment type				
Government	167 (11.5)	59 (17.9)	226 (12.7)	<0.001
Private	134 (9.2)	116 (35.2)	250 (14.1)	
Self	633 (43.6)	61 (18.3)	694 (38.9)	
student	118 (8.1)	23 (6.9)	141 (7.9)	
Unemployed	309 (21.3)	64 (19.4)	373 (20.9)	
Missing data	91 (6.3)	7 (2.1)	98 (5.5)	
Marital status				
Divorced/Separate	115 (7.9)	26 (7.9)	141 (7.9)	0.527
Married	741 (51.0)	167 (50.6)	908 (50.9)	
Single	340 (23.4)	94 (28.5)	434 (24.4)	
Widowed	165 (11.4)	37 (11.2)	202 (11.3)	
Highest education				
Missing data	91 (6.3)	6 (1.8)	97 (5.4)	0.001
NFE	197 (13.6)	38 (11.5)	235 (13.2)	
Primary	327 (22.5)	78 (23.6)	405 (22.7)	
Secondary	518 (35.7)	98 (29.7)	616 (34.6)	
Tertiary	319 (21.9)	110 (33.3)	429 (24.1)	
Missing data	91 (6.3)	6 (1.8)	97 (5.4)	
HBsAg				
Negative	887 (61.1)	213 (64.5)	1100 (61.7)	<0.001
Positive	220 (15.2)	34 (10.3)	254 (14.3)	
Missing	345 (23.8)	83 (25.2)	428 (24.1)	
HCV antib				
Negative	1006 (69.3)	211 (63.9)	1217 (68.3)	0.002
Positive	83 (5.7)	34 (10.3)	117 (6.6)	
Missing	363 (25)	85 (25.7)	448 (25.1)	

Table 1 continues…

Variable	Pre-test and treat 1452 (81.4%)[a]	Test and treat 330 (18.5%)[b]	All patients 1782 (100%)	P value [a] versus[b]
TB				
Negative	1397 (96.2)	298 (90.3)	1695 (95.1)	<0.001
Positive	55 (3.8)	32 (9.7)	87 (4.9)	
CD4+ cell count, cells/mm3				
≤100	471 (32.4)	95 (28.8)	566 (31.8)	<0.001
101-200	358 (24.7)	51 (15.5)	409 (23)	
201-350	365 (25.1)	92 (27.9)	457 (25.6)	
>350	229 (15.8)	92 (27.9)	321 (18)	
Missing data	29 (2)	0 (0)	29 (1.6)	
Viral load, copies/mL				
Median (IQR)	204 (102 - 338)	263 (111 - 507)	212(102-347)	<0.001
≤10,000	257 (24.6)	48 (24.8)	305 (24.8)	<0.001
10,001-100,000	336 (32.4)	61 (31.3)	397 (32.3)	
>100,000	443 (42.8)	86 (44.1)	529 (43.0)	
Missing data	416 (28.7)	135 (40.9)	551 (30.9)	
Median (IQR)	44634 (5604.5 - 242351.7)	48505 (6234.6 - 269033)	44677 (5630-728879)	0.857
Antiretroviral Regimen				
ABC/3TC/EFV	14 (0.9)	10 (3.0)	24 (1.4)	<0.001
ABC/3TC/NVP	11 (0.8)	0 (0)	11 (0.6)	
AZT/3TC/EFV	31 (2.1)	1 (0.3)	32 (1.8)	
AZT/3TC/NVP	503 (34.6)	13 (3.9)	516 (28.9)	
d4T/3TC/NVP	2 (0.1)	0 (0)	2 (0.11)	
TDF/3TC/NVP	207 (14.3)	0 (0)	207 (11.6)	
TDF/3TC/EFV	684 (47.1)	306 (92.7)	990 (55.5)	
NNRTI				
EFV	729 (50.2)	317 (96.1)	1046 (58.7)	<0.001
NVP	723 (49.8)	13 (3.9)	736 (41.3)	
NRTI				
AZT	534 (36.9)	14 (4.2)	548 (30.7)	<0.001
ABC	25 (1.7)	10 (3.1)	35 (1.9)	
TDF	893 (61.5)	306 (92.7)	1199 (67.3)	

ABC= abacavir, AZT= zidovudine, 3TC = lamivudine, EFV = efavirenz, NVP = nevirapine, TDF = tenofovir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor.

Regarding baseline clinical characteristics, a higher proportion of patients were co-infected with HBV in the pre-test and treat era, while HCV co-infection was higher during the test and treat era. More patients were also co-infected with TB at baseline during the test and treat era than in the pre-test and treat period. The median baseline CD4 cell count was higher in the test and treat group than in the pre-test and treat group. Baseline viral load at treatment initiation was also higher in the test and treat participants than in the pre-test and treat participants.

The dominant ARV regimen during the test and treat era was tenofovir/lamivudine/efavirenz (TDF/3TC/EFV), while less than half of patients initiated treatment with this regimen in the pre-test and treat era.

Additionally, almost all patients (96%) initiated EFV-based ART during the test and treat era, compared to 50% in the pre-test and treat period. These findings are summarized in Table 1.

Immunologic outcomes and associated factors

A negative relationship between change from baseline CD4+ cell count levels and pre-ART treatment CD4+ cell count was observed (Figure 1). Of the patients (1020) with CD4 count results at 12-months of ART, a significantly higher proportion of patients had early immunologic failure in the "test and treat" era compared to the pre- "test and treat" era (308 out of 838; 37% for the pre- "test and treat" versus 106 out 182; 58% for the "test

and treat" era, p <0.001).

The results of the multivariable logistics regression presented in Table 2 revealed that the "test and treat" era was associated with 5.88 times higher odds of early immunological failure compared to the pre-"test and treat" era. Other significant factors that increased the odds of early immunologic failure included treatment with NVP-based ART (OR-2.20; 95% CI- 1.3-3.71) and initiation of ART with a CD4+ cell count of greater than 350 cells/mm3 (OR-2.57; 95% CI- 1.52-4.35).

Table 2: Logistic regression analysis of factors associated with immunologic failure at 12 months of ART

	Adjusted odds ratio (95% C.I. for odds ratio)	P value
Post-test and treat vs. pre-test and treat	5.88 (3.29 -10.52)	<0.001
Females vs. males	1.11 (0.73 - 1.69)	0.62
Age, Years	1.00 (0.98 - 10.2)	0.71
NNRTI		
NVP vs. EFV	2.20 (1.30 - 3.71)	<0.001
NRTI		
AZT vs. TDF	0.63 (0.39 - 1.03)	0.07
ABC vs. TDF	0.35 (0.02 - 6.00)	0.47
HBsAg Negative	0.83 (0.53 - 1.30)	0.42
HCVAb Negative	1.05 (0.58 - 1.90)	0.87
CD4 +cell count, cells/mm^3		
101-200 vs. ≤100	.40 (0.24 - 0.68)	0.001
201-350 ≤100	.76 (0.47 - 1.23)	0.24
>350 vs. ≤100	2.57 (1.52 - 4.35)	<0.001
Viral load, copies/mL		
10,0001-10^5 vs. ≤10^4	1.29 (08.2 - 2.03)	0.28
>10^5 vs. ≤10^4	1.15 (0.72 - 1.84)	0.56

Variables with significant association with virologic failure are displayed in bold font style.

Virologic outcomes and associated Factors

Although the difference was not statistically significant, the proportion of participants with virologic failure at 12 months after starting ART was higher in the "test and treat" arm compared to the pre-"test and treat" arm (135 out of 242; 56% versus 136 out of 258; 53%; p = 0.049). In the multivariable analysis (Table 3), participants in the "test and treat" era had three times greater odds of early virologic failure compared to patients in the pre-"test and treat" era (OR-2.63; 95% CI-1.38-5.02). The odds of early virologic failure was 69% lower in participants co-infected with hepatitis C virus (OR=0.31; 95% CI-0.14-0.67). Additionally, participants who initiated ART at viral load levels greater than 10,000 copies/mL had three times greater odds of early virologic failure compared to patients with viral load <10,000 copies/mL (OR-3.01; 95% CI- 1.57-5.80).

Table 3: Logistic regression analysis of factors associated with virologic failure

Baseline characteristics and treatment groups	Adjusted odds ratio	P value
Test and treat vs. Pre-test and treat	3.46 (1.70 - 7.01)	<0.001
Females versus males	1.31 (0.72 - 2.38)	0.37
Age, years	1.00 (0.97 - 1.02)	0.79
NNRTI backbone		
NVP vs. EFV	2.04 (0.83 - 1.26)	0.15
NRTI backbone		0.91
AZT vs. TDF	1.04 (0.47 - 2.23)	0.93
ABC vs. TDF	1.60 (0.17 - 14.87)	0.68
HBsAg Negative	0.70 (0.36 - 1.37)	0.30
HCVAb positive	0.31 (0.14 - 0.67)	0.003
CD4 cell count, cells/mm^3		
101-200 vs. ≤100	1.36 (0.63 - 2.92)	0.43
201-350 ≤100	0.89 (0.41 - 1.93)	0.77
>350 vs. ≤100	0.84 (0.41 - 1.73)	0.64
Viral load, copies/mL		
10,0001-10^5 vs. ≤10^4	2.63 (1.38 - 5.02)	0.003
>10^5 vs. ≤10^4	3.01 (1.57 - 5.80)	<0.001

Variables with significant association with virologic failure are displayed in bold font style

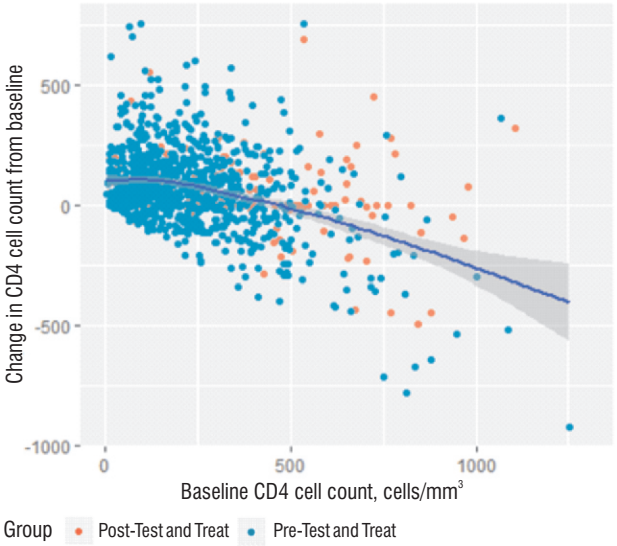

Figure 1: Relationship between baseline CD4+ cell count and change in CD4+ cell count at 12 months of ART.

Discussion

We analyzed the outcomes of patients who started antiretroviral therapy (ART) in two different eras: pre-"test and treat" and post-"test and treat". Specifically, we compared the rates of immunological improvement and virologic failure at 12 months after starting ART. After controlling for other factors that could influence the

outcomes, we found that patients in the post-"test and treat" era had a six-fold higher likelihood of early immunological failure and a three-fold higher likelihood of early virologic failure compared to those in the pre-"test and treat" era.

Our study found a negative correlation between the change in CD4+ cell count levels and the pre-ART treatment CD4+ cell count, indicating that patients who initiated ART with higher CD4+ cell counts in the "test and treat" era had lower changes in CD4+ cell count from baseline compared to those who initiated ART in the "pre-test and treat" era with lower CD4+ cell counts. This trend was also reported in an earlier study of over 35,000 Nigerian patients in a PEPFAR-supported program.[13-14] The study found that the median change in CD4+ cell count at six months of ART was lowest in patients with the highest baseline CD4+ cell count. This trend may be responsible for the higher proportion of patients with early immunologic failure in the "test and treat" era compared to the pre-"test and treat" era. Even after accounting for other factors, a high baseline CD4+ cell count remained a predictor of early immunological failure. Further research is needed to understand the clinical and biological reasons behind this pattern.

This study showed that compared to EFV-based ART, patients initiated on NVP-based ART were about three times more likely to have early immunological failure. This result is in agreement with the results of a previous study in Ethiopia in which treatment naïve patients initiated on EFV-based regimens showed more likelihood of immunologic recovery compared to those initiated on NVP-based regime. Other studies have however found that immunologic responses were comparable between NVP- and EFV-based regimens. [15] Whether the observed differences between EFV-based and NVP-based ART observed in this study in early immunological response persist in the long-term will be the subject of further studies. Moreover, NVP-based ART is no longer the preferred first-line regimen according to the 2016 Nigeria HIV treatment guideline.[10]

The proportion of patients with early virologic failure was higher in the "test and treat" era compared to the pre- "test ant treat" era, although, the difference was not significant. However, after adjustment for confounders, the odds of virologic failure was increased three times for patients in the "test and treat" era compared to the pre- "test and treat" era. These results are consistent with that of other studies, supporting the belief that patients who initiated ART at higher CD4+ cell count are less likely to be adherent to treatment and hence have poorer early virologic outcomes. This result could be attributed, in part, to inadequate preparation before starting ART, which may have been due to the pressure to adhere to the recommended "test and treat" guidelines.[13] Additionally, many patients may not have experienced any symptoms at the time of ART initiation and may not have understood the importance of adhering to the treatment regimen, which could have resulted in poor adherence to ART.[13] Meloni et al [14] in an earlier study found that early average adherence was lower in patients with baseline CD4+ cell counts >350 cells/mm^3 as compared to those patients with counts <350 cells/mm.[3] This finding was corroborated in another study by Grimsrud et al,[16] who found that patients with baseline CD4+ cell counts ≤300 cells/mm^3 were more likely to be lost to follow-up after 24 months on ART than those patients with CD4+ cell counts of 150–199mm.[3]

The higher likelihood of early virologic failure among patients in the "test and treat" era compared to the "pre-test and treat" era is supported by results of other studies. In multicenter cohort study by Meloni et al, a higher relative hazard of virologic failure was found for patients with baseline CD4+ cell count >350 cells/mm^3 compared with those with baseline CD4+ cell count of 201–350 cells/mm.[3,14] In another study by Eshleman et al,[17] that compared effect of early versus delayed ART on virologic outcomes in 1,566 participants, virologic failure at 12 months was strongly associated with higher CD4+ cell count at ART initiation. These results emphasize the need for re-orientation towards a strong focus on treatment adherence in the "test and treat" era to support a high level of adherence and promote favourable immunologic and virologic outcomes.

This study has some strengths; the findings presented reflect real-life HIV management practices and patients' experiences with regards to immunological improve-ment and viral suppression rates in a resource-limited setting. The regular measurement of CD4+ cell count and viral load is a major strength of the study. This allowed for an assessment of early treatment outcomes. Viral load measurement is one of the WHO recommended strategies for monitoring of treatment failure. Despite the strengths of our study, one major limitation of the study was that it is a single institutional study. Hence, extrapolation of the study results to other settings should be done with caution. Secondly, due to the retrospective nature of the study, there were instances of missing data on certain variables. For specific outcomes such as immunological and virological outcomes, the study only analyzed data of those with available data, which could increase the chance of survivor bias. Additionally, it has been noted there exist variations in patients CD4 count aside from those arising from inflammation and other comorbidity like liver disease.[18-20]

Conclusion

Overall, a high proportion of patients in this setting had immunologic and virologic failure at 12 months of ART.

In our setting, the "test and treat" strategy resulted in poorer early immunologic improvement and viral suppression compared to the CD4+ cell count-guided treatment initiation. Re-orientation towards ongoing treatment adherence and promoting the message of "undetectable equals untransmissible" (U=U) is recommended in the "test and treat" era, with additional interventions needed to improve its effectiveness, particularly in resource-limited settings.

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