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ORIGINAL RESEARCH

Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons

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Background

The European AIDS Clinical Society (EACS) guidelines are intended for all clinicians involved in the care of HIV-positive persons, and are available in print, online, and as a free App for download for iPhone and Android.

Guideline highlights

The 2015 version of the EACS guidelines contains major revisions in all sections; antiretroviral treatment (ART), comorbidities, coinfections and opportunistic diseases. Among the key revisions is the recommendation of ART for all HIV-positive persons, irrespectively of CD4 count, based on the Strategic Timing of AntiRetroviral Treatment (START) study results. The recommendations for the preferred and the alternative ART options have also been revised, and a new section on the use of pre-exposure prophylaxis (PrEP) has been added. A number of new antiretroviral drugs/drug combinations have been added to the updated tables on drug–drug interactions, adverse drug effects, dose adjustment for renal/liver insufficiency and for ART administration in persons with swallowing difficulties. The revisions of the coinfection section reflect the major advances in anti-hepatitis C virus (HCV) treatment with direct-acting antivirals with earlier start of treatment in individuals at increased risk of liver disease progression, and a phasing out of interferon-containing treatment regimens. The section on opportunistic diseases has been restructured according to individual pathogens/diseases and a new overview table has been added on CD4 count thresholds for different primary prophylaxes.

Conclusions

The diagnosis and management of HIV infection and related coinfections, opportunistic diseases and comorbidities continue to require a multidisciplinary effort for which the 2015 version of the EACS guidelines provides an easily accessable and updated overview.

Keywords: EACS, Guidelines, HIV, antiretroviral treatment, ART, HBV, HCV, opportunistic infections, comorbidities

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The European AIDS Clinical Society (EACS) philosophy and methodology

The EACS is a nonprofit organization that aims to promote excellence in standards of care, research and

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education in HIV infection and related coinfections, and to actively engage in the formulation of public health policy, with the aim of reducing HIV disease burden across Europe [1].

The overall scope of the EACS guidelines is hence to provide easily accessible recommendations to clinicians centrally involved in the care of HIV-positive individuals. Importantly, the guidelines are not to be considered as a full overview of all aspects of HIV infection, for which we refer to more elaborate work, but rather as a continuously updated overview of the most relevant clinical issues in HIV infection.

The EACS guidelines were first published in 2005 and are currently available in print, online on the EACS website (http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html) and, since 2015, as a free App for download for iPhone and Android. The guidelines are revised annually for the electronic versions, and biennally for the printed version, and released during the EACS Conference. While the guidelines are developed by European HIV experts and were initially targeted primarily at European clinicians, the use of the guidelines has in recent years been more widely spread, and the guidelines are therefore now translated into more than 10 different languages [2].

The EACS guidelines consist of five main sections, including a general table overview of all major issues in HIV infection as well as more detailed recommendations on antiretroviral treatment (ART), diagnosis, monitoring and treatment of comorbidities, coinfections and opportunistic diseases. Only drugs currently licensed by the European Medicines Agency (EMA) are taken into consideration in the guidelines.

Each respective section (I–V) of the guidelines is managed by a panel of experienced European HIV experts, and additional experts, where needed, (e.g. the Comorbidity section), and governed by a three-person leadership group consisting of a Panel Chair, Co-chair and Young scientist. Furthermore, the guidelines are managed by a guidelines Coordination Chair and Coordinator Assistant from the Center for Health and Infectious Disease Research (CHIP) in Copenhagen, Denmark, who work closely with the EACS secretariat in Brussels, Belgium. Each panel leadership group is responsible for the annual content revision of their section and will convene with other panels where there are potential overlaps between panels. Once all panels have finalized their revisions, these are extensively cross-reviewed by the remaining panels and by the Guidelines Coordinating Chair and Assistant for consistency. A team of linguistics, translators and layout designers/typesetters then take over to produce the final version of the guidelines to be released into the public domain.

All recommendations provided in the EACS guidelines are evidence-based whenever possible, and, based on expert opinions in the rare instance where adequate evidence is unavailable. A list of the main references used is provided as a separate section of the guidelines. All panel members have declared their interests, which are available upon request.

EACS guidelines version 8.0

In the 2015 revision of the EACS guidelines [3], major revisions have been made in almost all sections. Most notably in the ART section the recommendations of when to start ART were changed based on the new results of the Strategic Timing of Antiretroviral Treatment (START) study [4] (Table 1), and the coinfection section was revised to reflect the major advances in anti-hepatitis C virus (HCV) treatment with the use of direct-acting antivirals (DAAs) phasing out use of interferon (IFN)-containing treatment. The following paragraphs describe, in more detail, the most important changes made in each section of the guidelines.

ART section

When to start: ART is now recommended for all HIV-positive persons, irrespectively of the CD4 count. The main reasons for this change in recommendation are the results of the START trial showing more favourable clinical outcomes among HIV-positive persons initiating ART at high CD4 counts as compared with persons initiating ART at lower CD4 counts [2]. Along with this change, the recommendations of what to start have also been changed in the new version of the guidelines.

What to start: Preferred regimens have been reduced from 13 to six options: four integrase inhibitor (INSTI)-based, one non-nucleoside reverse transcriptase inhibitor (NNRTI)-based, and one ritonavir-boosted protease inhibitor (PI/r)-based (Table 2). Changes are mainly based

Table 1 Recommendations for initiation of antiretroviral therapy (ART) in HIV-positive persons with chronic infection without prior ART exposure*

Symptomatic HIV disease (CDC B or C conditions, including tuberculosis)	Asymptomatic HIV infection	
	Current CD4 count	
Any CD4 count	<350 cells/μL	≥350 cells/μL
SR	SR	R

CDC, Centers for Disease Control and Prevention; SR, strongly recommended; R, recommended.
*The table is modified from the European AIDS Clinical Society (EACS) guidelines version 8.0.

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Table 2 Initial combination regimen for ART-naïve adult HIV-positive persons. (A) Recommended regimens (one of the following to be selected)*,†. (B) Alternative regimens (to be used when none of the preferred regimens are feasible or available, whatever the reason)

Regimen	Dosing	Food requirement	Caution
A			
2 NRTIs + INSTI			
ABC/3TC/DTG‡,§	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2 h after or 6 h before).
TDF/FTC0¶,** + DTG	TDF/FTC 300¶¶/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	None	
TDF/FTC/EVG/c¶,††,**	TDF/FTC/EVG/c 300¶¶/200/150/150 mg, 1 tablet qd	With food	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2 h after or 6 h before).
TDF/FTC¶,** + RAL	TDF/FTC 300¶¶/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2 h after or 6 h before).
2 NRTIs + NNRTI			
TDF/FTC/RPV¶	TDF/FTC/RPV 300¶¶/200/25 mg, 1 tablet qd	With food (min 390 kcal required)	Only if CD4 count > 200 cells/μL and HIV VL < 100,000 copies/mL. PPI contraindicated; H2 antagonists to be taken 12 h before or 4 h after RPV.
2 NRTIs + PI/r			
TDF/FTC¶,** + DRV/r	TDF/FTC 300¶¶/200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy.
B			
2 NRTIs + INSTI			
ABC/3TC‡,§ + RAL	ABC/3TC 600/300 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2 h after or 6 h before)
2 NRTIs + NNRTI			
ABC/3TC‡,§ + EFV ‡‡	ABC/3TC 600/300 mg, 1 tablet qd + EFV 600 mg, 1 tablet qd	At bed time or 2 h before dinner	
TDF/FTC/EFV¶,**	TDF/FTC/EFV 300¶¶/200/600 mg, 1 tablet qd	At bed time or 2 h before dinner	
2 NRTIs + PI/r or PI/c			
ABC/3TC‡,§ + ATV/r	ABC/3TC 600/300 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Co-administration with PPI is contraindicated¶¶
TDF/FTC¶,** + ATV/r	TDF/FTC 300¶¶/200 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + RTV 1 tablet 100 mg qd	With food	
ABC/3TC‡,§ + ATV/c	ABC/3TC 600/300 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	
TDF/FTC¶,** + ATV/c	TDF/FTC 300¶¶/200 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	Co-administration with PPI is con-traindicated.§§ eGFR < 70 mL/min: combination not recommended.
ABC/3TC‡,§ + DRV/r	ABC/3TC 600/300 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + RTV 1 tablet 100 mg qd	With food	Monitor in persons with a known sulfonamide allergy.
ABC/3TC‡,§ + DRV/c	ABC/3TC 600/300 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	
TDF/FTC¶,** + DRV/c	TDF/FTC 300¶¶/200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy. eGFR < 70 mL/min: combination not recommended.
TDF/FTC¶,** + LPV/r	TDF/FTC 300¶¶/200 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid	With food	Use with caution in persons with high cardiovascular risk

on the results of trials with regimens containing INSTIs. The Panel also considered that at least one regimen containing a PI/r and one containing an NNRTI should be listed as 'preferred' treatment options.

Post-exposure prophylaxis (PEP): Based on the results of the PARTNER study, the recommendations on PEP for sexual exposure to HIV were revised to reflect the fact that, if an HIV-positive source person has documented undetectable plasma HIV-RNA, PEP is no longer recommended. Use of tenofovir (TDF)/emtricitabine (FTC) + raltegravir or boosted darunavir is now also recommended as an ART regimen for PEP.

Pre-exposure prophylaxis (PrEP): A brand new section on PrEP has been added to the guidelines. PrEP (TDF/

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Table 2 (*Continued*)

Regimen	Dosing	Food requirement	Caution
Other combinations			
3TC[§] + LPV/r	3TC 300 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid	With food	
RAL[§] + DRV/r	RAL 400 mg, 1 tablet bid +DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Only if CD4 count > 200 cells/μL and HIV-VL < 100,000 copies/mL. Co-administration of antacids containing Al or Mg not recommended.

*Only drugs currently licensed for initiation of therapy by the EMA are taken into consideration (in alphabetical order).
†Generic HIV drugs are becoming more available and can be used as long as they replace the same drug and do not break recommended fixed dose combinations.
‡ABC contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk (> 20%).
§Use this combination only if HBs Ag negative.
¶Avoid TDF if osteoporosis, renal monitoring required, see page 45.
**If TDF/FTC is not available, one alternative could be TDF+3TC as separate entities.
††TDF/FTC/EVG/c use only if eGFR > 70 mL/min. It is recommended that TDF/FTC/EVG/c is not initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment.
‡‡EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains.
§§If PPI co-administration is judged unavoidable, consider an alternative regimen; if given, dose increase of ATV to 400 mg qd may be considered, close clinical monitoring is recommended and doses of PPI comparable to omeprazole 20 mg should not be exceeded and must be taken approximately 12 h prior to the ATV/r. H2 antagonists to be taken 12 h before or 4 h after ATV.
¶¶In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the concentration of the active metabolite.

FTC) should be recommended for high-risk men who have sex with men (MSM) and transgender individuals and considered for high-risk heterosexual men and women. Both continuous and 'on demand' options are discussed as possible approaches.

Comorbidity section

Ageing and comorbidities: A closer attention was brought to the growing proportion of HIV-positive individuals with advanced age and multiple simultaneous comorbidities, who may benefit most from a multidisciplinary assessment. As such intensified monitoring of renal function is now recommended in individuals with an estimated glomerular filtration rate (eGFR) < 90 mL/min and with progressively declining eGFR. The use of a chronic kidney disease risk equation is also recommended. Furthermore, screening for depression is now encouraged more widely because of its high prevalence, recommendations for smoking cessation have been further elaborated and recommendations for regular assessment of liver disease in individuals with viral hepatitis coinfection with ultrasound and fibrosis staging have been added.

New drugs/drug combinations: A number of new antiretroviral drugs/drug combinations have been included in the revised tables on drug–drug interactions, adverse effects, and dose adjustment for renal/liver insufficiency and in the table on administration of ART in individuals with swallowing difficulties. Several of these tables have, in previous version of the EACS guidelines, been available exclusively in the electronic version; however, as a result of requests from the guideline users, the tables on dose adjustment for renal/liver insufficiency and administration of ART in individuals with swallowing difficulties are now also available in the print version.

Drug–drug interactions: Two new drug–drug interaction tables on interactions with corticosteroids and contraceptive drugs with the use of ART have been included in the 2015 version of the guidelines.

Cardiovascular disease (CVD) risk factors: In the general population, several guidelines on risk factors (e.g. dyslipidaemia) for CVD have ceased to use threshold values. However, the Comorbidity panel have in the revised version kept threshold values for all CVD risk factors to aid everyday clinical practice.

Vaccination: A general recommendation to avoid polysaccharide vaccination has been added, as has a recommendation for influenza and *Streptococcus pneumonia* vaccination in all HIV-positive persons.

Coinfection section

Treatment of hepatitis B virus (HBV) infection: The guideline text and tables now reflect the general recommendation to start ART in the presence of HBV coinfection regardless of the CD4 count. ART should contain TDF as a dually active agent against HIV and HBV infection.

Treatment of chronic HCV infection: Analogous to the situation for HBV, the guideline text and tables now also reflect the general recommendation to start ART in the presence of HCV coinfection regardless of the CD4 count. A stronger emphasis is placed on IFN-free treatment regimens (Table 3) as well as earlier start of DAA

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Table 3 Hepatitis C virus (HCV) treatment options in HCV/HIV coinfected persons*

IFN-free HCV treatment options				
		Treatment duration and ribavirin usage		
HCV GT	Treatment regimen	Noncirrhotic	Compensated cirrhotic	Decompensated cirrhotic CTP class B/C
1 and 4	SOF + SMP + RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV[(i)]	Not recommended
	SOF/LDV + RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV in cirrhotics or pre-/post-transplant[(i)]	
	SOF + DCV + RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV in cirrhotics or pre-/post-transplant[(i)]	
	OBV/PTV/r + DSV	12 weeks in GT 1b	Not recommended	
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	12 weeks in GT 1b 24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4	24 weeks in GT 4	Not recommended
2	SOF + DCV + RBV	12 weeks without RBV	12 weeks with RBV	12 weeks with RBV
	SOF + RBV	12 weeks	16–20 weeks[(ii)]	
3	SOF + PEG-IFN/RBV	Not recommended	12 weeks in persons eligible for PEG-IFN	Not recommended
	SOF + RBV	24 weeks	Not recommended	
	SOF + DCV + RBV[(iii)]	12 weeks without RBV	24 weeks with RBV	
5	SOF/LDV	12 weeks without RBV	12 weeks without RBV	
6	In the absence of clinical data on DAAs in HCV GT 6 infection persons should be treated similarly to those with HCV GT 1 and 4 infection			

CTP, Child-Turcotte-Pugh, DAA, direct-acting antiviral; RBV, ribavirin; SOF, sofosbuvir; SMP, simeprevir; DCV, daclatasvir; LDV, ledipasvir; OBV, ombitasvir; PEG, pegylated; PTV/r, paritaprevir/ritonavir; DSV, dasabuvir; IFN, interferon, GT, genotype.
[(i)]Cirrhotic persons with negative predictors of response can be treated for 24 weeks with RBV (negative predictors: treatment-experienced, platelet count $< 75 \times 10^3$ cells/μL).
[(ii)]Possible extension up to 16 weeks in treatment-naïve cirrhotic persons or relapsers; up to 20 weeks in treatment-experienced cirrhotic persons.
[(iii)]Based on expert opinion and preliminary data from studies in persons on pre-marketing expanded access programmes.
*The table is modified from the European AIDS Clinical Society (EACS) guidelines version 8.0.

treatment in cases where there is a risk of liver disease progression. All detailed recommendations on IFN-containing regimens have therefore been removed from the main HCV treatment section. Acknowledging that IFN-containing treatment is still being used in certain countries, recommendations on IFN-containing treatment have been collected in an addendum available online. Text and tables have furthermore been updated following the licensing of sofosbuvir/ledipasvir and AbbVie 3D combo. The drug–drug interaction table on DAAs and antiretrovirals has subsequently also been updated.

Treatment of acute HCV infection: In the absence of randomized, controlled data on the use of DAAs in the setting of acute HCV coinfection, treatment with pegylated IFN and ribavirin should be based on an individual decision, weighing the known toxicities and long treatment duration against a potentially strong patient wish for early HCV cure, particularly in HIV-positive MSM with a higher risk of HCV transmission and in countries where the cost of DAAs will only be reimbursed in chronic HCV infection with advanced fibrosis.

Opportunistic diseases section

While the overall content of this section has not undergone major changes, the structure has changed considerably. In previous versions of the guidelines, the recommendations for opportunistic diseases were subdivided into three overview tables on primary prophylaxis, treatment and secondary prophylaxis/maintenance treatment. In the 2015 version, the recommendations are now structured according to the individual pathogens/diseases to ease the overview. Now, each section contains a short abstract on diagnostics for each opportunistic disease. Additionally, a new overview table on CD4 count thresholds as indication for different primary prophylaxes has been added. The section on *Cryptococcosis* has been complemented with a recommendation for pre-emptive treatment.

New tables: Entirely new tables with recommendations on treatment of progressive multifocal leukoencephalopathy (PML), histoplasmosis, cryptosporidiosis and cystoisosporiasis have been added.

Conclusions

The diagnosis and management of HIV infection and related coinfections, opportunistic diseases and comorbidities continue to require a multidisciplinary effort for which the 2015 version of the EACS guidelines provide an easily assessable and updated overview.

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