TITLE PAGE

TITLE: Essentials from the 2015 European AIDS Clinical Society (EACS) Guidelines for the Treatment of Adult HIV-positive Persons

RUNNING HEAD: EACS Guidelines 2015

AUTHORS: Lene Ryom[1], Christoph Boesecke[2,] Valentin Gisler[3], Christian Manzardo[4], Jürgen K Rockstroh[2], Massimo Puoti[5], Hansjakob Furrer[3], Jose M Miro[4], Jose M Gatell[4], Anton Pozniak[6], Georg Behrens[7], Manuel Battegay[8]and Jens D Lundgren[1] on behalf of the EACS Executive Committee

1 CHIP, Rigshospitalet, Dept. of Infectious Diseases, Section 2100, Finsencentret, University of Copenhagen Denmark

2 Department of Medicine, University of Bonn, Germany

3 Department of Infectious Diseases, Bern University Hospital and University of Bern, Switzerland

4 Infectious Diseases Service, Hospital Clinic, University of Barcelona, Spain

5 Department of Infectious Diseases, AO Ospedale Niguarda Ca' Granda, Milan, Italy

6 HIV Directorate, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom

7 Medizinische Hochschule Hannover, Klinik für Immunologie und Rheumatologie , Germany

8 Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel, Switzerland

CORRESPONDING AUTHOR

Lene Ryom, M.D., PhD.

CHIP, Rigshospitalet, Dept. of Infectious Diseases, Section 2100, Finsencentret, University of Copenhagen

Blegdamsvej 9,

DK-2100 Copenhagen O

Tel: + 45 35 45 57 65/ Fax: +45 35 45 57 57/ email: lene.ryom.nielsen@regionh.dk

TEXT COMMENTARY

The EACS Philosophy and Methodology

EACS is a non-profit organization aiming at promoting excellence in standards of care, research and education in HIV infection and related co-infections, 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 easy accessible recommendations to clinicians centrally involved with 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.

The EACS guidelines were first published in 2005 and are currently available in print, online at the EACS website (http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html) and from 2015 as a free App for download for iPhone and Android. The guidelines are revised annually for the electronic versions, and biannual for the printed version, and released during the EACS Conference. Whilst the guidelines are developed by European HIV-experts and 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 ten different languages (2).

The EACS guidelines consist of five main sections including a general table overview of all major issues in HIV as well as more detailed recommendations on antiretroviral treatment (ART), diagnosing, monitoring and treatment of co-morbidities, co-infections and opportunistic diseases. Only drugs currently licensed by the 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 where needed additional experts, e.g. in the co-morbidity 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 guideline Coordination Chair and Assistant from CHIP, Center for health and Infectious disease research, in Copenhagen Denmark working 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 were there are potential overlaps in-between panels. Once all panels have finalised their revisions these are extensively cross-reviewed by the remaining panels and by the

Coordinating Chair and Assistant for consistency. A team of linguistics, translators and layout/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 in the rare instance where adequate evidence is unavailable, based on expert opinions. A list of the main references used is provided as a separate section of the guidelines. All Panel members have declared their interest, which are available upon request.

EACS Guidelines Version 8.0

In the 2015 revision of the EACS guidelines (3) major revision have been made in almost all sections, the antiretroviral treatment (ART) section most notably have changed recommendations of when to start ART based on the new results of the START study (4), and the co-infection section is revised to reflect the major advances in anti-HCV treatment with direct-acting antivirals (DAAs) phasing out 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 from the START trial showing more favourable clinical outcomes among HIV-positive persons initiating ART at high CD4 counts as compared to 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 guideline version.

Table 1 Recommendations for Initiation of ART in HIV-positive Persons with Chronic Infection without Prior ART Exposure[1]

Symptomatic HIV disease (CDC B or C conditions, incl. tuberculosis)	Asymptomatic HIV infection	
Any CD4 count	Current CD4 count	
	<350	≥350
SR	SR	R

SR = Strongly Recommended R = Recommended

1.Table modified from the EACS guidelines version 8.0

What to start: Preferred regimens have been reduced from thirteen 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 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 a NNRTI should be listed as 'preferred' treatment options.

Table 2. Initial Combination Regimen for ART-naive Adult HIV-positive Persons[1]

A) Recommended Regimens (One of the following to be selected, in alphabetic order)

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC/DTG(i, ii)	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	Any time	Co-administration of antacids, containing Al, Ca or Mg is not recommended. DTG 50 mg bid with rifampicin
TDF/FTC(iii, iv) + DTG	TDF/FTC 300/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	Any time	
TDF/FTC/EVG/c(iii, iv)	TDF/FTC/EVG/c 300/200/150/150 mg, 1 tablet qd	With food	Co-administration of antacids, containing Al, Ca or Mg is not recommended
TDF/FTC(iii, iv) + RAL	TDF/FTC 300/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	Any time	Co-administration of antacids, containing Al, Ca or Mg is not recommended. RAL 400 or 800 mg bid with rifampicin
2 NRTIs + NNRTI			
TDF/FTC/RPV(iii)	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 12h before or 4h after RPV
2 NRTIs + PI/r			
TDF/FTC(iii, iv) + 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) Alternative Regimens (to be used when none of the preferred regimens are feasible or available, whatever the reason)

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC(i, ii) + RAL	ABC/3TC 600/300 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	Any time	Co-administration of antacids, containing Al, Ca or Mg is not recommended. RAL 400 or 800 mg bid with rifampicin
2 NRTIs + NNRTI			
ABC/3TC(i, ii) + EFV (vi)	ABC/3TC 600/300 mg, 1 tablet qd + EFV 600 mg, 1 tablet qd	At bed time or 2 hours before dinner	
TDF/FTC/EFV(iii, iv)	TDF/FTC/EFV 300/200/600 mg, 1 tablet qd	At bed time or 2 hours before dinner	
2 NRTIs + PI/r or PI/c			
ABC/3TC(i, ii) + 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.(vii)
TDF/FTC(iii, iv) + 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(i, ii) + 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(iii, iv) + 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 contraindicated.(vii) eGFR <70 mL/min: combination not recommended.
ABC/3TC(i, ii) + 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(i, ii) + 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[iii, iv] + 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[iii, iv] + 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
Other combinations			
3TC[ii] + LPV/r	3TC 300 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid	With food	
RAL[ii] + 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.

1. Table modified from the EACS guidelines version 8.0

i ABC contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counseling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk (>20%).
ii Use this combination only if HBs Ag negative
iii Avoid TDF if osteoporosis, renal monitoring required.
iv If TDF/FTC is not available, 1 alternative could be TDF + 3TC as separate entities.
v EVG/c/TDF/FTC: use only if eGFR ≥ 70 ml/min. It is recommended that EVG/c/TDF/FTC not be initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment.
vi EFV: not to be given if history of suicide attempts or mental illness; not recommended to be initiated in pregnant women or women with no reliable and consistent contraception; continuation is possible if EFV is already started before pregnancy; not active against HIV-2 and HIV-1 group O strains.
vii 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 hours prior to the ATV/r. H2 antagonists to be taken 12h before or 4h after ATV.

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 that if an HIV-positive source person has documented undetectable plasma HIV-RNA, PEP is no longer recommended. Uses of tenofovir/emtricitabine + raltegravir or boosted-darunavir are now also recommended as ARV regimens for PEP.

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

Co-morbidity section

Ageing and co-morbidities; A highlight was added on the growing proportion of HIV-positive individuals with advanced age and multiple simultaneous co-morbidities, that may benefit the most from a multidisciplinary assessment. As such, intensified monitoring of renal function was 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 equations is also recommended. Furthermore, screening for depression is now encouraged more widely due to the high prevalence, recommendations for smoking cessation were further elaborated and recommendations for regular assessment of liver disease in individuals with viral hepatitis co-infection with ultrasound and fibrosis staging were added.

New drugs /drug combinations; A number of new antiretroviral drugs/drug combinations were included in the revised tables on drug-drug interaction, adverse effect, dose adjustment for renal/liver insufficiency and in the table for 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 due to 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 have been included in the 2015 guidelines on interactions with corticosteroids and contraceptive drugs with use of ART.

Cardiovascular diseases (CVD) risk factors; In the general population several guidelines on risk factors (i.e. dyslipidemia) for CVD have ceased to use threshold values. However the Co-morbidity Panel have in the revised version kept threshold values for all CVD risk factors to aid everyday clinical practise.

Vaccination: A general recommendation to avoid polysaccharide vaccination was added, as was a recommendation of influenza and *streptococcus pneumonia* vaccination in all HIV-positive persons.

Co-infections

Treatment of HBV: the guideline text and tables now reflect the general recommendation to start ART in the presence of HBV co-infection regardless of the CD4 count. ART should contain tenofovir as a dually active agent against HIV and HBV infection.

Treatment of chronic HCV: Analogous to HBV guideline text and tables now also reflect the general recommendation to start ART in the presence of HCV co-infection regardless of the CD4 count. A stronger emphasis is put on IFN-free treatment regimens (Table 3) as well as earlier start of DAA treatment in cases where there is risk of liver disease progression. As such, all detailed recommendations on IFN-containing regimens have 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 of DAAs and ARVs has subsequently also been updated.

Table 3. HCV Treatment Options in HCV/HIV Co-infected Persons[1]

IFN-free HCV Treatment Options				
HCV GT	**Treatment regimen**	**Treatment duration & ribavirin usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 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 without 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 HCV GT 1 and 4 infection			

1. Table modified from the EACS guidelines version 8.0

RBV = Ribavirin
SOF = Sofosbuvir
SMP = Simeprevir
DCV = Daclatasvir
LDV = Ledipasvir
OBV = Ombitasvir
PTV/r = Paritaprevir/Ritonavir
DSV = Dasabuvir
IFN= Interferon

[i] Cirrhotic persons with negative predictors of response can be treated 24 weeks with RBV (negative predictors: treatment-experienced, platelet count <75x10^3 cells/uL)

[ii] Possible extension up to 16 weeks in treatment-naïve cirrhotics or relapsers; up to 20 weeks in treatment-experienced cirrhotics

[iii] Based on expert opinion and preliminary data from studies in persons on pre-marketing expanded access programs

Treatment of acute HCV: In the absence of randomized, controlled data on the use of DAAs in the setting of acute HCV co-infection 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 DAAs will only be reimbursed in chronic HCV with advanced fibrosis.

Opportunistic diseases

Whilst 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. Newly, each section contents 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 was complemented by a recommendation for pre-emptive treatment.

New tables: Entirely new tables with recommendations on treatment of Progressive Multifocal Leukoencephalopathy (PML), Histoplasmosis, Cryptosporidiosis and Cystoisosporiasis were added.

Conclusion

The diagnosis and management of HIV infection and related co-infections, opportunistic diseases and co-morbidities continue to require a multidisciplinary effort for which the 2015 version of the EACS guidelines provides an easy assessable and updated overview.

REFERENCES

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EACS Guidelines Panel Members;

Jens D Lundgren (Guideline Chair and Coordinator), Lene Ryom (Assistant Coordinator)

HIV Treatment: Jose M Gatell (Chair), Anton Pozniak (Vice-chair), Christian Manzardo (Young scientist), Antonella d´Arminio Monforte, José Arribas, Manuel Battegay, Nathan Clumeck, Nikos Dedes, Anna Maria Geretti, Andrzej Horban, Christina Katlama, Jens D Lundgren, Sheena McCormack, Jean-Michel Molina, Cristina Mussini, François Raffi, Peter Reiss, Hans-Jürgen Stellbrink.

Co-morbidity: Jens D Lundgren (Chair), Georg Behrens (Vice-chair), Lene Ryom (Young scientist), Manuel Battegay, Mark Bower, Paola Cinque, Simon Collins, Juliet Compston, Gilbert Deray, Stéphane De Wit, Christoph A Fux, Giovanni Guraldi, Patrick Mallon, Esteban Martinez, Catia Marzolini, Socrates Papapoulos, Renaud du Pasquier, Neil Poulter, Peter Reiss, Alessandra Vigano, Ian Williams, Alan Winston.

Co-infections: Jürgen K Rockstroh (Chair), Massimo Puoti (Vice-chair), Christoph Boesecke (Young Scientist), Sanjay Bhagani, Raffaele Bruno, Svilen Konov, Karine Lacombe, Stefan Mauss, Luis Mendao, Lars Peters, Andri Rauch, Cristina Tural.

Opportunistic diseases: Hansjakob Furrer (Chair), Jose M Miro (Vice-chair), Valentin Gisler (Young scientist), Paola Cinque, Gerd Fätkenheuer, Ole Kirk; Amanda Mocroft, Philippe Morlat, Anton Pozniak, Alain Volny-Anne.

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