Appendix 1

Updated Embase search strategy



Supplementary Table 1. Characteristics of studies investigating the prevalence of vertebral fracture in patients living with HIV

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Population | Time period | Design | Fracture evaluation | PLHIV (n) | % men PLHIV | Age PLHIV | Prevalence of VF (%) | Evidence level |
| Atteritano 2018 1 | Messina University Hospital | 2012-2015 | Cross-sectional | Lateral spine X-ray | 100 | 16% | 44 | 16% | III |
| Borderi 2014 2 | Infectious Diseases unit of Bologna | 2011-2012 | Cross-sectional | Lateral spine X-ray | 202 |  | 51 | 23% | III |
| Ciulini 2017 3 | Sant Andrea Hospital | 2013 | Cross-sectional | Lateral spine X-ray | 143 | 87% | 43 | 14% | III |
| Gazzola 2015 4 | San Paolo Hospital, Milan | 2007-2011 | Cross-sectional | Lateral spine X-ray | 194 | 73% | 49 | 21% | III |
| Llop 2018 5 | HIV/AIDS unit | 2014-2016 | Cross-sectional | Lateral spine X-ray | 128 | 73% | 57 | 20% | III |
| Mata-Marin 2018 6 | Outpatient clinic | 2015-2016 | Cross-sectional | Lateral spine X-ray | 104 | 87% | 49 | 25% | III |
| Pietogrande 2012 (abstract) 7 | Milano | N/A | Cross-sectional | MorphoXpress | 133 | N/A | 47 | 21% | III |
| Porcelli 2014 8 | Clinic of Infectious and Tropical Diseases of Brescia | 2009-2012 | Cross-sectional | Lateral spine X-ray | 131 | 71% | 51 | 27% | III |
| Stephens 2014 9 | VA Medical Center, Atlanta | 2007-2010 | Cross-sectional | Lateral spine X-ray | 232 |  | 49.1 | 47% | III |
| Thouvinen 2014 10 | ANRS EP48 HIV CHEST cohort | 2011-2012 | Cross-sectional | Chest Low dose CT | 397 | 83% | 49.5 | 12% | III |
| Torti 2012 11 | Department of Infectious Diseases, Brescia | 1998-2010 | Cross-sectional | Lateral Chest X-ray | 160 | 100% | 53 | 27% | III |
| Yin 2010 12 | CUMC and BLHC | 2002-2007 | Cross-sectional | Spine radiographs | 92 | 0% | 55.9 | 4·1% | III |

Age (years) and BMI (kg/m2) are presented as means. Level of evidence based on level of evidence for prognostic studies.

Body mass index (BMI),patients living with HIV (PLHIV), vertebral fracture (VF)

Supplementary Table 2. Characteristics of studies investigating fracture risk in patients living with HIV

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Population | Time period | Design | Fracture evaluation | PLHIV (n) | % men PLHIV | Age of PLHIV | BMI of PLHIV | Evidence level |
| Arnsten 2007 13 | CHAMPS study | 2000-2006 | Cohort | Incident fractures | 328 | 100% | 54.7 |  | II |
| Battalora 2016 14 | HOPS-DIDX and SUN study, site Denver | 2004-2012 | Cohort | Incident fractures | 1,006 | 83% | 43 |  25 | II |
| Bedimo 2012 15 | VHA Clinical Case registry | 1988-2009 | Cohort | Incident fractures | 56,600 |  | 44-46 |  | I |
| Byrne 2015 16 | Medicaid | 1999-2007 | Cohort | Incident-hip fracture | 96,253 | 62% | 41 |  | I |
| Collin 2009 17 | ANRS CO APROCO COPILOTE cohort | 1997-2007 | Cohort | Incident fractures - grade 3 or 4 fractures | 1,281 | 77% | 36.2 |  22 | II |
| Gedmintas 2014 18 | Research Patient Data Registry | 2001-2012 | Cohort | Incident fracture | 3,161 | 73% | 41-44  | II |
| Gedmintas 2017 19 | Research Patient Data Registry | 2001-2012 | Cohort | Incident fracture | 2,663 | 72% | 43 | 26 | II |
| Gonciulea 2017 20 | MACS | 1984-2015 | Cohort | Incident fracture (self-report) | 1,221 | 100% | 40 | 25 | II |
| Guerri-Fernandez 2013 21 | SIDIAP | 2007-2009 | Cohort | Incident fracture | 2,489 | 75% | 50 | 25 | I |
| Hansen 2012 22 | DHCS and DNHR | 1995-2010 | Cohort | Incident fracture | 5,306 | 76% | 36.7 |  | I |
| Komatsu 2018 23 | HRD survey | 2004-2013 | Cohort | Incident fracture | 3,251 | 94 | 40-41.2 | I |
| LaFleur 2018 24 | VHA | 2003-2015 | Cohort | Incident fracture | 7,161 | 94-97% | 47-50 | 25-27 | I |
| Mundy 2012 25 | INBD | 1997-2008 | Case-control | Incident fracture | 2,477 (C) 9,144 (CO) | 67-72% | III |
| Nkhoma 2016 26 | Truven Health MarketScan Databases | 2008-2014 | Cohort | Incident fracture | 9,876 | 84-89%  | 42- 44 | II |
| Peters 2013 27 | Guy's and St Thomas Hospital, London | 2009-2010 | Cross-sectional | Previous fracture | 222 | 60% | 44-46  | 24-28  | III |
| Prieto-Alhambre 2014 28 | DNHR | 2000 | Case-control | Incident | 102 |  |  |  | III |
| Prior 2007 29 | CWHS and CaMOS | 2001-2003 | Case-control | Life-time fragility fractures | 138 | 0% | 38 | 25 | III |
| Reyes 2014 30 | SIDIAP | 2007-2009 | Cohort | Incident | - | - | - | - | II |
| Sharma 2015 31 | WIHS | 2002-2013 | Cohort | Incident | 1,713 | 0% | 40 | 29 | II |
| Short 2013 32 | UK Teaching Hospital | 2008 | Cross-sectional | Prevalent/previous | 168 | 100% | 45 | 25 | III |
| Triant 2008 33 | RPDR | 1996-2008 | Cross-sectional | Prevalence | 8525 | 65% |  |  | III |
| Warriner 2010 (abstract) 34 | Medical claims | 1999-2010 | Cohort | Incident | 13,221 |  |  |  | II |
| Womack 2011 35 | VACS-VC | 1997-2009 | Cohort | Incident | 40,115 | 100% |  | 25 | I |
| Womack 2013 36 | VACS-VC | 1997-2009 | Cohort | Incident | 40,115 |  | 46 | 25 | I |
| Yin 2010 37 | WIHS | 2002-2008 | Cohort | Incident | 1,728 | 0% | 40 | 29 | II |
| Yin 2012 38 | ALLRT Database | -2009 | Cohort | Incident | 4,640 | 83% | 39 | 25 | II |
| Yin 2016 39 | VACS-VC | 2000-2010 | Cohort | Incident | 7,067 | 100% | 56 | 25 | II |
| Yong 2011 40 | The Alfred Hospital, Melbourne | 1998-2009 | Case-control | Incident | 2,424 | 89% | 50 | 23 (C) 25(CO) | II |
| Young 201141 | HOPS and NHAMCS | 2000-2008 | Cohort | Incident | 5,826 | 79% | 40 | 24 | II |

Age (years) and BMI (kg/m2) are presented as means. Level of evidence based on level of evidence for prognostic studies.

Body mass index (BMI), cases (C), controls (CO), patients living with HIV (PLHIV)

Supplementary Table 3. Characteristics of studies reporting bone mineral density in patients living with HIV and controls

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Design | ART | PLHIV (n) | CO (n) | PLHIV (%men) | CO (%men) | Age PLHIV | Age CO | BMI PLHIV | BMI CO | Evidence level |
| Amiel 2004 42 | Cross-sectional | Mixed | 148 | 81 | 100% | 100% | 40 | 39 | 23 | 24 | III |
| Anastos 2007 43 | Cross-sectional | ART naive | 74 | 152 | 0% | 0% | 43 | 36 | 29 | 30 | III |
| Anastos 2007 43 | Cross-sectional | Non-PI ART | 98 | 152 | 0% | 0% | 42 | 36 | 27 | 28 | III |
| Anastos 2007 43 | Cross-sectional | PI ART | 93 | 152 | 0% | 0% | 44 | 36 | 28 | 28 | III |
| Arnsten 2006 44 | Cross-sectional | Mixed | 263 | 232 | 0% | 0% | 44 | 45 |  |  | III |
| Arnsten 2007 13 | Cohort | Mixed | 328 | 231 | Mix | Mix | 55 | 56 |  |  | III |
| Badie 2013 45 | Cross-sectional | Naive | 44 | 40 | 84% | 78% | 35 | 37 | 23 | 23 | III |
| Badie 2013 45 | Cross-sectional | ART | 36 | 40 | 75% | 78% | 39 | 37 | 23 | 23 | III |
| Bedimo 2016 46 | Cross-sectional | ART | 81 | 107 | 100% | 100% | 56 | 53 | 28 | 30 | III |
| Biver 2014 47 | Cross-sectional | ART | 28 | 112 | 100% | 100% | 64 | 65 | 25 | 26 | III |
| Bolland 2007 48 | Cohort | ART | 23 | 26 | 100% | 100% | 47 | 45 | 24 | 25 | III |
| Bolland 2012 49 | Cohort | ART | 32 | 33 | 100% | 100% | 49 | 46 | 25 | 26 | III |
| Brown 2004 50 | Cross-sectional | ART | 51 | 22 | 86% | 82% | 40 | 39 | 25 | 26 | III |
| Bruera 2003 51 | Cross-sectional | Naive | 33 | 31 | 91% | 77% | 31 | 31 | 24 | 25 | III |
| Bruera 2003 51 | Cross-sectional | Non-PI ART | 35 | 31 | 69% | 77% | 35 | 31 | 24 | 25 | III |
| Bruera 2003 51 | Cross-sectional | PI + ART | 42 | 31 | 81% | 77% | 36 | 31 | 24 | 25 | III |
| Calmy 2013 52 | Cross-sectional | ART | 22 | 44 | 0% | 0% | 44 | 44 | 22 | 22 | III |
| Dolan 2007 53 | Cross-sectional | Mixed | 28 | 100 | 0% | 0% | 39 | 41 | 19 | 27 | III |
| Dolan 2007 53 | Cross-sectional | Mixed | 124 | 100 | 0% | 0% | 41 | 41 | 26 | 27 | III |
| Guerri-Fernandez 2016 54 | Cross-sectional | Naive | 50 | 35 | 70% | 69% | 37 | 34 | 24 | 23 | III |
| Hamill 2013 55 | Cross-sectional | Non ART | 74 | 98 | 0% | 0% | 34 | 30 | 28 | 27 | III |
| Hamill 2013 55 | Cross-sectional | Pre ART | 75 | 98 | 0% | 0% | 33 | 30 | 24 | 27 | III |
| Hamill 2017 56 | Cohort | Naive | 120 | 67 | 0% | 0% | 33-35 | 31 |  26-28.  | 29 | III |
| Hileman 2014 57  | Cohort | Naive | 47 | 41 | 70% | 6% | 40 | 37 | 26 | 27 | III |
| Jones 2008 58 | Cross-sectional | Mixed | 57 | 47 | 60% | 30% | 61 | 62 | 26 | 29 | III |
| Kalyan 2018 59  | Cross-sectional | Mixed | 73 | 280 | 0% | 0% | 43 | 50 | 25 | 26 | III |
| Loiseau-Peres 2002 60 | Cross-sectional | Mixed | 31 | 31 | 100% | 100% | 43 |  |  |  | III |
| Loiseau-Peres 2002 60 | Cross-sectional | Mixed | 16 | 16 | 0% | 0% | 38 |  |  |  | III |
| Madeddu 2004 61 | Cross-sectional | ART +PI | 98 | 64 | 65% |  | 38 |  |  |  | III |
| Madeddu 2004 61 | Cross-sectional | ART | 60 | 64 | 63% |  | 38 |  |  |  | III |
| Mulligan 2012 62 | Cross-sectional | ART +PI | 105 | 53 | 100% | 100% | 21 | 21 |  |  | III |
| Mulligan 2012 62 | Cross-sectional | ART | 42 | 53 | 100% | 100% | 21 | 21 |  |  | III |
| Mulligan 2012 62 | Cross-sectional | Naive | 52 | 53 | 100% | 100% | 21 | 21 |  |  | III |
| Negredo 2014 63 | Cross-sectional | Mixed | 232 | 75 | 79% | 73% | 28 | 26 |  |  | III |
| Paul 2010 64 | Cross-sectional | Naive | 35 | 35 | 100% | 100% | 39 | 39 |  |  | III |
| Paul 2010 64 | Cross-sectional | ART | 35 | 35 | 100% | 100% | 38 | 39 |  |  | III |
| Peters 2013 27 | Cross-sectional | Mixed | 222 | 222 | 60% | 80% | 45-46 | 45-47 | 24-28  | 25-27  | III |
| Prior 2007 29 | Case-control | Mixed | 138 | 402 | 0% | 0% | 38 | 38 | 25 | 26 | III |
| Sharma 2015 65 | Cohort | Mixed | 246 | 219 | 0% | 0% | 47 | 48 | 28 | 32 | III |
| Teichmann 2009 66 | Cross-sectional | Naive | 32 | 20 | 100% | 100% | 39 | 35 | 24 | 26 | III |
| Teichmann 2009 66 | Cross-sectional | Naive | 48 | 20 | 100% | 100% | 35 | 35 | 25 | 26 | III |
| Unsal 2017 67 | Cross-sectional | Mixed | 65 | 23 | 39% | 48% | 24 | 25 | 24 | 25 | III |
| Yin 2010 68 | Cross-sectional | Mixed | 92 | 95 | 0% | 0% | 56 | 60 | 28 | 30 | III |
| Yin 2014 69 | Cross-sectional | ART | 30 | 14 | 100% | 100% | 23 | 22 | 26 | 25 | III |
| Yin 2005 70 | Cross-sectional | Mixed | 31 | 186 | 0% | 0% | 56 | 57 | 26 | 28 | III |
| Zhang 2013 71 | Prospective cohort | Naive | 40  | 40 | 88% | 88% | 37 | 37 | 22 | 23 | III |

Age (years) and BMI (kg/m2) are presented as means. Level of evidence based on level of evidence for prognostic studies. The same study may be present several times as it may report on different PLHIV populations (e.g. naïve vs. ART experienced).

Antiretroviral theraphy (ART), Body mass index (BMI), control (CO), patients living with HIV (PLHIV) protease inhibitor (PI)

Supplementary Table 4. RCTs and cohort studies investigating longitudinal changes of BMD in PLHIV

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Population | Time period | Design | ART | PLHIV (n) | PLHIV (%men) | Age PLHIV | PLHIV BMI | Evidence level |
| RCTs investigating TAF and TDF |  |  |  |  |  |  |
| Arribas 201772\* | 2 phase 3 trails | - | RCT | Naive randomized to TAF or TDF | 1,733 | 85% | 33-35 | 24-25 | Ib |
| Eron 2018 73 | AMBER | - | RCT | Naive randomized to TAF or TDF  | 113 | 88% | 34 | - | Ib |
| Mills 2015 74 | Multicenter phase 2 study | 2012-2014 | RCT | Naive randomized to TAF or TDF, both with DRV/C/FTC. Single tablet regimen | 153 | 93% | 33 | - | Ib |
| Mills 2016 75 | GS-US-292-0109 (phase 3 non-inferiority trial) | 2013-2015 | RCT | Virologically suppressed randomized to switch from TDF to TAF or stay on one of four TDF-based regimen | 1,436 | 89-90% | 40-41 | 26 | Ib |
| Post 2017b76 | - | - | RCT | Virologically suppressed randomized to switch from FTC/TDF to FTC/TAF back-bone evaluated by third agent (boosted PI vs unboosted third agent) | 633 | 85% | 49 | - | Ib |
| Raffi 2017 77 | GS-US-311-108 Double-blind phase 3 trial | 2014-2016 | RCT | Switch to TAF or stay on TDF | 663 | 84-86% | 49 | 26 | Ib |
| Sax 2014 78\* | GS-US-292-0102 (phase 2 multicenter study) | 2011-2013 | RCT | Naive randomized to TDF vs TAF | 1,733 | 96-98% | 34-38 | - | Ib |
| Wohl 2016 79\* | GS-US-292-0104/0111 | - | RCT | Naive randomized to TAF vs TDF | 1,733 | 85% | 33-35 | 24-25 | Ib |
| RCTs investigating abacavir and TDF |  |  |  |  |  |  |  |
| Erlandson 2013 80 | A5224s, sub-study of A5202  | 2005-2008 | RCT | Naive randomized to ABC or TDF | 269 | 85% | 38 | 26 | Ib |
| Grant 2015 81 | ACTG A5224s and ASSERT  | 2005-2008 | Post-hoc of RCT | Naive randomized to TDF or ABC | 652 | 83% | 38 | 25 | Ib |
| Gupta 2017 82 | ACTG A5224s | 2005-2008 | RCT | Naive randomized to TDF or ABC | 269 | 85% | 38 | - | Ib |
| McComsey 2011 83 | A5224s, sub-study of A5202  | 2005-2008 | RCT | Naive randomized to ABC/3TC or TDF/FTC with open-label EFV or ATV/ r | 269 | 85% | 38 | - | Ib |
| Moyle 201384 | ASSERT study | 2007-2009 | RCT | Naive randomized to ABC/3TC vs TDF/FTC, + EFV | 385 | 81% | 37 | - | Ib |
| Negredo 2014 85 | OsteoTDF study | 2010-2012 | RCT | Virologically suppressed randomized to stay on TDF or switch to ABC | 48 | 79-89% | 49 | 22-24 | Ib |
| Rasmussen 2012 86 | SWAP study | 2008-2010 | RCT | Switch from ZDV to ABC or TDF  | 40 | 55-70% | 46-50 | 25 | Ib |
| Stellbrink 2010 87 | ASSERT study | 2007-2009 | RCT | Naive randomized to ABC or TDF | 385 | 81% | 37 | - | Ib |
| Other RCTs and cohort studies |  |  |  |  |  |  |  |
| Assoumou 2013 88 | ANRS 120 Fosivir trial | - | Cohort | ART | 94 | 100% | 46 | 22 | II |
| Bernadino 2015 89 | NEAT001/ANRS143 | 2010-2011 | RCT | Naive randomized to RAL or TDF | 152 | 89-95% | 39-40 | 23 | Ib |
| Bloch 2014 90 | Hospital | - | Cohort | TDF switched to RAL | 37 | 97% | 49 | 26 | II |
| Bolland 2007 48 | Infectious disease clinics | - | Cohort | ART | 23 | 100% | 47 | 24 | II |
| Bolland 2012 | Infectious disease clinics 49 | - | Cohort | ART | 32 | 100% | 49 | 25 | II |
| Bonjoch 2010 91 | HIV unit | 2000-2009 | Cohort | ART (1% naive) | 391 | 72% | 42 | 23 | II |
| Briot 2011 92 | Monark | 2003-2005 | RCT | Naive randomized to LPV/r or LPV+ZDV | 68 | 64-70% | 26-38 | 23-24 | Ib |
| Brown 2015 93 | A5260s, substudy of AIDS Clinical Trial Group A5257 | 2009-2013 | RCT | Naive randomized to TDF or RAL | 328 | 89-91% | 36-37 | 24-26 | Ib |
| Calza 2017 94 | Infectious disease clinic | 2011-2015 | Cohort | ART | 38 | 71% | 46 | - | II |
| Casado 2016 95 | Hospital | 2012-2014 | Cohort | TDF switched to RAL | 90 | 80% | 48 | 24 | II |
| Cook 2016 96 | Single HIV clinic | 2011-2015 | RCT | Naive randomized to TDF or RAL | 20 | 60-80% | 30-37 | 24-27 | Ib |
| Cotter 2013 97 | Substudy of PREPARE study | 2006-2008 | RCT | Switch to TDF or remain on ZDV | 53 | 75-93% | 45-47 | 23-24 | Ib |
| Duviver 2009 98 | ANRS 121 substudy | 2003-2005 | RCT | ART | 71 | 77% | 40 | 23 | Ib |
| Gallant 2004 99 | Multicenter study | 2000-2004 | RCT | Naive randomized to TDF or stavudine | 600 | 74-75% | 36 | - | Ib |
| Galli 2016 100 | MODAt | 2010-2014 | RCT | ATV/r monotherapy vs ATV/r triple therapy | 69 | 82-86% | 41 | 23-24 | Ib |
| Grund 2009 101 | SMART study | 2002-2006 | RCT | Mixed | 214 | 81% | 44 | 26 | Ib |
| Guerri-Fernandez 2018 102 | Consecutively recruited | - | Cohort | Naive starting on TDF | 40 | 83% | 38 | 24 | II |
| Hamill 2017 56 | Single center study | 2010-2011 | RCT | Naive initiating ART (>85% TDF) | 120 | 0% | 33-35 | 26-28 | Ib |
| Hansen 2011103 | SPAR trial substudy | 2006-? | RCT | Naive randomized to ZDV + EFV or LPV/r + EFV | 59 | 90% | 43 | 22 | Ib |
| Haskelberg 2014 104 | The Second-Line study (phase IV multicenter study) | 2010-2013 | RCT | Randomized to RAL+LPV/r or 2-3 NRTI + LPV/r  | 210 | 48% | 39 | 23 | Ib |
| Hileman 2014 57 | Single Immunology Unit | 2010-2013 | Cohort | Naive  | 47 | 70% | 40 | 26 | II |
| Hoy 2017 105 | START Bone Mineral Density Substudy | 2011-2015 | RCT | Naive randomized to initiating treatment vs deferring ART (to CD4 < 350) | 399 | 74% | 32 | 24 | Ib |
| Koga 2016 106 | Hospital | 2010-2015 | Cohort | ART | 54 | 100% | 42 | 23 | II |
| Madeddu 2014 107 | HIV University Care Center | - | Cohort | ART | 51 | 53% | 40 | - | II |
| Martin 2013 108 | The Second-Line study | 2010-2013 | RCT | Adults virologically failing standard first-line therapy randomized to RAL and LPV/r vs standard second line therapy (LPV/r + 2-3 N(t)RTIs) | 210 | 48% | 39 | - | Ib |
| Mondi 2015 109 | ATLAS study | - | Cohort | Virologically suppressed simplification trial from three-drug ATV/r + 2 NRTIs based regimen to dual regimen of ATV/r + 3TC | 40 | 58% | 45 | - | II |
| Post 2017 110 | Multicenter phase 3 study (GS-US-292-0112) | 2013-2016 | Cohort | Virologically suppressed switched from baseline treatment (65% including TDF) to E/C/FTC/TAF  | 242 | - | 58 | - | II |
| Pozniak 2017 111 | GS-US-292-0112 (open-label phase 3 study) | 2013-2014 | Cohort | Switch to TAF | 242 | 79% | 58 | - |  |
| Rey 2015 112 | Single center study | 2003-2010 | Cohort | Naive commencing a first ARV treatment (76,2% TDF) | 50 | 100% | 39-40 | 22-23 | II |
| Rivas 2008 113 | Single center study | 2002-2005 | Cohort | Naive initiating ZDV/3TC + ABC or LPV/r | 32 | 100% | 39-44 | 23 | II |
| Rockstroh 2013114 | GS-US-236-0103 (phase 3 study) | - | RCT | Naive randomized to E/C/FTC/TDF vs ATV/r + FTC/TDF | 708 | - | - | - | Ib |
| Saitz 2018 115  | Boston ARCH prospective cohort study | 2012-2014 | Cohort | Mixed | 234 | 64% | 50 | 26 | II |
| Sharma 2012 116 | Metabolic substudy of WIHS (Women's Interagency HIV Study) | 2001-2009 | Cohort | Mixed | 318 | 0% | 44 | 27 | II |
| Sharma 2010 117  | CHAMPS study | 2002 | Cohort | Mixed | 230 | 100% | 55 | 26 | II |
| Sharma 2015 65 | Menopause Study | 2001-2005 | Cohort | Mixed | 246 | 0% | 47 | 28 | II |
| Tinago 2017 118 | HIV UPBEAT Study group | 2012-2015 | Cohort | Mixed | 176 | 61% | 39 | - | II |
| Van Vonderen 2009 119 | MEDICLAS study | 2003-2007 | RCT | Naive randomized to LPV/r with ZDV/3TC or NVP | 48 | 100% | 38-43 | 23 | Ib |
| Yin 2012 120 | Single center study | 2002-2008 | Cohort | Mixed | 73 | 0% | 56 | 28 | II |
| Zhang 2013 71 | Single center study | 2007-2012 | Cohort | Naive initiating ART | 40 | 88% | 37 | 22 | II |

Age (years) and BMI (kg/m2) are presented as means. Level of evidence based on level of evidence for prognostic studies

Abacavir (ABC), atazanavir (ATV), atazanavir/ritonavir (ATV/r), antiretroviral theraphy (ART), body mass index (BMI), cobicistat (C), darunavir (DRV), efavirenz (EFV), elvitegravir (E), emtricitabine (FTC), lamivudine (3TC), lopinavir (LPV), lopinavir/ritonavir (LPV/r), nevirapine (NPV), nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), patients living with HIV (PLHIV), protease inhibitor (PI), raltegravir (RAL) randomized controlled trial (RCT), tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), Zidovudine (ZDV),

\* These three studies report on the same population and only one study is included in the meta-analysis.

Supplementary Table 5. Characteristics of studies investigating antiosteoporotic treatment in patients living with HIV.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Design | BMD /osteoporosis status at baseline | Antiosteoporotic treatment | PLHIV (n) | PLHIV (%men) | Age PLHIV | Result | Evidence level |
| Alendronate |  |  |  |  |  |  |  |  |
| McComsey 2007 121 | RCT | T-score < -1.4 | 70 mg alendronate weekly vs placebo both + calcium and vitamin D for 48 weeks.  | 82 | 71% | 48 | Alendronate significantly improved BMD at the lumbar spine and total hip. | Ib |
| Mondy 2005 122 | RCT | Osteopenia or osteoporosis | 70 mg alendronate weekly vs no study drug both + calcium and vitamin D for 48 weeks. | 31 | 87% | 44 | Alendronate significantly improved BMD at the lumbar spine no difference at total hip | Ib |
| Rozenberg 2012 123 | RCT | Osteoporosis | 70 mg alendronate weekly vs placebo both + calcium and vitamin D for 96 weeks. | 44 | 45% | 43-47 | Alendronate significantly improved BMD at the lumbar spine but not total hip  | Ib |
| Zoledronate |  |  |  |  |  |  |  |  |
| Bolland 2007 124 | RCT | T-score < -0.5 | Annual iv zoledronate(two doses) or placebo + calcium and vitamin D for 2 years. | 43 | 100% | 49-50 | Zoledronate significantly increased BMD at the lumbar spine and hip. | Ib |
| Bolland 2008 125 | Cohort | T-score < -0.5 | Follow up of Bolland 2007. No treatment in follow up period. | 33 | 100% | 50 | Zoledronate significantly increased BMD at the lumbar spine and hip after 36 months. | II |
| Bolland 2012 126 | Cohort | T-score < -0.5 | Four year extension of Bolland 2007. No treatment in follow up period. | 43 | 100% | 49-50 | The effect of zoledronate persists after five years.  | II |
| Hoy 2018 127 | RCT | T-score < -1.0 | Continue TDF and start zoledronate or switch from TDF to another active antiretroviral therapy for 24 months.  | 87 | 93-100% | 49-51 | Zoledronate and TDF significantly increased BMD at the total hip and lumbar spine compared to switch after 12- and 24 months. | Ib |
| Negredo 2014 128 | RCT | T-score < -1.0 | Randomized to 1 or 2 doses of zoledronate or control. | 21 | 78-91% | 46-49 | Zoledronate significantly improved BMD at lumbar spine. No difference between 1 and 2 doses. | Ib |
| Ofotokun 2016 129 | RCT | Non-osteoporotic | ART initiation (TDF containing) randomized to zoledronate or placebo for 48 weeks. | 63 (ART naïve) | 79% | 39-40 | Zoledronate significantly improved BMD at lumbar spine. | Ib |
| Risedronate |  |  |  |  |  |  |  |  |
| Pepe 2014 130 | Cohort | Two groups 1) osteoporosis and osteopenia with fractures 2) normal or osteopenia without fractures | Risedronate twice monthly 12 months in group 1. Both groups with calcium and vitamin D. | 41 | 100% | 44-53 | Risedronate significantly increased lumbar spine BMD in group 1. Better response in eugonadal men compared to hypogonadal men.  | II |

Age (years) is presented as a mean. Level of evidence based on level of evidence for prognostic studies

Bone mineral density (BMD), patients living with HIV (PLHIV), randomized controlled trial (RCT)

Supplementary Table 6. Guidelines identified for the management of osteoporosis in patients living with HIV.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Source | Whom to screen | Repeat screening | Whom to treat | Treatment | Dose | Duration of treatment |
| Osteo Renal Exchange Program,131 | Individuals 40-50 year old with FRAX score >10%, all ≥ 50 year old, all using glucocorticoids or history of fragility fracture or high risk of falls  | 1) T-score -1·01 to -1·99 in 5 years.2) T-score -2·00 to -2·49 or started on bisphosphonates 1-2 years. | 1) Hip or vertebral fracture 2) T-score between -1·0 and -2·5 and FRAX score ≥ 20 % or 3 ≥ at the hip 3) T-score≤-2·5 at FN, TH or LS  | Consider bisphosphonate therapy. Ensure calcium and vitamin D intake. Lifestyle advice.If on TDF recommended switching to abacavir or raltegravir.  | 70 mg alendronate once weekly or 5 mg zoledronate yearly. | Reassess indication for bisphosphonates in 3-5 years. |
| McComsey 2010 132 | ≥ 50 years males and postmenopausal women and/or history of fracture. | 1) T-score >-1 and no fragility fracture in 2-5 years. 2) T-score -1·01 to -2·49 and no fragility fracture 1-2 years. 3) T-score ≤-2·5 or fragility fracture 1-2 years. | T-score ≤-2·5 or fragility fracture. | Consider bisposphonate or other treatment. |  |  |
| Bolland 2015 133 | On stable ART: Age >65-70 years or strong risk factors for fracture. | Periodically reassess fracture risk decided by baseline risk. |  |  |  |  |
| BHIVA 2016 134 | Screening by FRAX in ≥ 50 years males and postmenopausal women or in the presence of other risk factors. |  |  |  |  |  |
| European AIDS Clinical Society guidelines 9.0 2017 135 | ≥ 50 years males and postmenopausal women and/or history of fracture. Clinical hypogonadism, high risk of falls, oral corticosteroid use. Also consider classic risk factors. Lateral spine X-rays if low BMD in the spine (osteoporosis) or height loss/kyphosis. |  | By national/geographical guidelines. Consider bisphosphonate in postmenopausal women and men >50 years with T-score ≤-2·5 and history of fragility fracture. | TAF should be considered as first choice over TDF in case of osteoporosis / progressive osteopenia or risk factor |  | Reassess indication for bisphosphonates in 3-5 years. |
| Negredo 2016 136 | ≥ 50 years males and postmenopausal women and/or history of fracture. Clinical hypogonadism, high risk of falls, oral corticosteroid use. Persons aged 40-50 years and FRAX >10 %. | Osteoporosis: Every 2 years. Osteopenia every 5 years. | 1) T-score between -1·0 and -2·5 and FRAX score ≥ 20 % or 3 ≥ at the hip 2) T-score≤-2·5 at FN, TH or LS | Alendronate or zoledronate. Avoiding or switching from TDF or protease inhibitors to others such as abacavir or integrase inhibitors. | 70 mg alendronate once weekly or 5 mg zoledronate yearly. |  |
| HIV Medicine Association/Infectious Diseases Societyof America 2013 137  | ≥ 50 years males and postmenopausal women. |  |  |  |  |  |

Antiretroviral treatment (ART), bone mineral density (BMD), femoral neck (FN), lumbar spine (LS), tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), the fracture risk assessment tool (FRAX), total hip (TH)

Supplementary Figure 1. Prevalence of vertebral fracture, by the mean age of patients living with HIV.

Supplementary Figure 2. Bone mineral density (g/cm2) at the lumbar spine compared between patients living with HIV and controls.

Supplementary Figure 3. Bone mineral density (g/cm2) at the hip compared between patients living with HIV and controls.



Supplementary Figure 4. Longitudinal changes in BMD (% change) within one year compared to baseline in patients living with HIV naive to ART treatment and initiating treatment. Lumbar spine (A), total hip (B).

A B

Supplementary Figure 5. Longitudinal changes in BMD (% change) within one year compared to baseline in patients living with HIV on stable ART treatment. Lumbar spine (A), total hip (B).

A



B

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Supplementary Figure 6. RCTs assessing the different impact of abacavir and TDF on BMD (% change) after 48 weeks in persons living with HIV. Lumbar spine (A), total hip (B).

A



B



Supplementary Figure 7. RCTs assessing the different impact of TAF and TDF on BMD (% change) after 48 weeks in persons living with HIV. Lumbar spine (A), total hip (B).

A



B



Supplementary Figure 8. RCTs assessing the effect of alendronate on BMD (% change) after 48 weeks at lumbar spine in persons living with HIV.



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